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TOPIC HIGHLIGHT

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Should capecitabine replace 5-fluorouracil in the first-line treatment of metastatic colorectal cancer?

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Abstract

Fluoropyrimidines play a central role in the first-line treatment of metastatic colorectal cancer. Our aim was to review whether capecitabine was a safer, non-inferior, economically superior and more convenient alternative to 5-fluorouracil. Capecitabine has previously been compared to 5-fluorouracil-either as a monotherapy or in combination with oxaliplatin, irinotecan, or biological drugs-and has been found to have comparable efficacy and safety profiles. Furthermore, pharmacoeconomic data and patients' preferences for oral chemotherapy further favor capecitabine. Therefore, capecitabine appears to be an effective and safe alternative to fluorouracil in the first-line treatment of metastatic colorectal cancer.

Key words: Capecitabine; 5-Fluorouracil; Metastatic colorectal cancer

Core tip: Although there is still controversy about whether capecitabine-based regimes can replace 5-fluorouracil (5-FU) in clinical practice in the treatment of first-line metastatic colon cancer, we have reviewed most of different randomized studies and meta-analyses, and we can conclude that capecitabine appear to be an effective, safe, convenient, and economically viable alternative to 5-FU.

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INTRODUCTION

Fluoropyrimidines play a central role in modern therapies directed toward the treatment of localized and metastatic colorectal cancer (mCRC). Since its introduction, fluorouracil (5-FU), an integral chemotherapeutic agent, has been frequently used as a monotherapy or as part of a combination therapy. Several notable advances in the use of 5-FU have improved patient outcomes. First, the limited response and safety profiles of a bolus infusion method were improved by moving to a continuous infusion method[1]. Second, the response rate and survival time exhibited an improvement of almost double when 5-FU administration was combined with the biomodulatory agent leucovorin (LV)[2].

Capecitabine, an orally administered tumor-activated 5-FU prodrug, was developed to improve tolerability and to reduce non-tumor cytotoxicity. Once administered in its inactive prodrug form, capecitabine is absorbed through the intestine and is converted to 5'-deoxy-5-fluorouridine (5'-DFUR) in the liver. Finally, the enzyme thymidine phosphorylase converts 5'-DFUR into the active form of 5-FU in both normal and tumor tissue; however,

Table 1 Comparison of treatment efficacy as a monotherapy

Clinical trial	Type	Treatments	ORR	PFS (mo)	OS (mo)
Van Cutsem *et al*[12] (2001)	Phase Ⅲ	Capecitabine *vs* 5-FU/LV	18.9% *vs* 15.0% (P = 0.013)	5.2 *vs* 4.7 (HR = 0.96, P = 0.65)	13.2 *vs* 12.1 (HR = 0.92, P = 0.33)
Hoff *et al*[11] (2001)	Phase Ⅲ	Capecitabine *vs* 5-FU/LV	24.8% *vs* 15.5% (P = 0.005)	4.3 *vs* 4.7 (HR = 1.03, P = 0.72)	12.5 *vs* 13.3 (HR = 1, P = 0.97)
Van Cutsem *et al*[13] (2004)	Integrated Analysis (Phase Ⅲ)	Capecitabine *vs* 5-FU/LV	26% *vs* 17% (P < 0.0002)	4.6 *vs* 4.7 (HR = 0.99, P = 0.95)	12.9 *vs* 12.8 (HR = 0.95, P = 0.48)

Capecitabine: 1250 mg/m^2 every 12 h (days 1-14), 3-wk regimen cycle; 5-FU/LV (Mayo clinic): 425 mg/m^2 5-FU bolus + LV 20 mg/m^2 (days 1-5), 4-wk regimen cycle. ORR: Overall response rate; PFS: Progression-free Survival; OS: Overall survival; HR: Hazard ratio; LV: Leucovorin.

the enzyme is present at higher concentrations within tumor cells[3]. This mode of action allows for greater tumor-targeting specificity, which consequently decreases systemic drug exposure.

The evolution of colon cancer treatment has led to the incorporation of several active drugs, such as irinotecan and oxaliplatin, which have been used in combination with 5-FU and capecitabine for improved survival outcomes. Furthermore, the addition of biological drugs in recent years (bevacizumab and cetuximab) has also led to improved results.

Despite the demonstrated efficacy of capecitabine in the first-line treatment of metastatic colon cancer, controversy remains regarding whether capecitabine-based regimens can replace 5-FU in clinical practice. Here, we present the efficacy and safety results of different randomized studies and meta-analyses. In addition, the suitability of oral treatment was assessed based on quality of life (QoL), patient preference, and cost analysis.

WHY SUBSTITUTE 5-FU WITH CAPECITABINE?

One of the major benefits provided by oral treatment is improvement in patients' QoL. It is well known that intravenous (*iv*) chemotherapy can have a negative impact on patient QoL, and it has been known to be associated with pain, discomfort, psychological stress, long hospital stays, and complications associated with venous catheters (such as thrombosis and infection)[4]. Therefore, the primary argument in favor of oral treatment compared to *iv* treatment is the convenience of home therapy and the concept that home therapy would result in an improved level of satisfaction[5].

One of the first studies to investigate patient preferences for palliative mCRC treatment found that more than 90% of patients preferred oral therapy, especially because it resolved problems associated with catheters, lessened the psychological impact of receiving treatment in a hospital, and reduced the numbers of visits to healthcare professionals[6]. However, it was also noted that two thirds of the study patients were not willing to sacrifice efficacy for QoL preferences, and almost 40% of patients did not wish to make the decision themselves. In a more recent randomized crossover trial, both oral capecitabine and *iv* 5-FU/LV were compared. Before the start of treatment, oral administration was almost completely preferred (95%), and after both treatment courses, the majority of patients (64%) still preferred orally delivered therapy; however, this preference was largely dependent on which *iv* scheme was employed[7]. Interestingly, a significantly better QoL (P < 0.05) was found using a 46-h continuous infusion of 5-FU (de Gramont outpatient regimen) compared to capecitabine-a result most likely attributable to reduced toxicity. This preference for treatment with an improved safety profile was also reported in a Danish study that compared capecitabine and 5-FU/LV bolus administration. The preference for *iv* treatment, it was argued, was due to the lower toxicity profile, thus reinforcing the concept that patient choice is strongly affected by toxicity and not convenience[8].

Because patients favor safety over convenience, if both treatments have equal safety profiles, then do patients prefer orally delivered therapy? A comparison of the non-inferior XELOX (1000 mg/m^2 oral capecitabine twice daily for 14 d; 2-h infusion of 130 mg/m^2 oxaliplatin on day 1; 3-wk regimen cycle) and FOLFOX-6 (2-h infusion of 100 mg/m^2 oxaliplatin, followed by 2-h infusion of 400 mg/m^2 LV, followed by 400 mg/m^2 bolus injection of 5-FU, followed by 46-h continuous infusion of 2400-3000 mg/m^2 5-FU; 2-wk regimen cycle) regimens[9] found that the group that received XELOX reported improved convenience and significant satisfaction with oral treatment, particularly because it reduced hospital visits (3.3 d *vs* 5.3 d, P = 0.045) and the number of daily activity hours lost (10.2 h *vs* 37.1 h, P = 0.007)[10]. Therefore, if capecitabine were shown to be non-inferior to continuous infusion 5-FU, would capecitabine replace 5-FU in the first-line treatment of mCRC?

CLINICAL DATA FOR THE REPLACEMENT OF 5-FU MONOTHERAPY BY CAPECITABINE AS THE FIRST-LINE TREATMENT FOR METASTATIC COLORECTAL CANCER

In two multicenter, open-label, phase Ⅲ comparison studies, capecitabine treatment was shown to be equivalent or superior to bolus 5-FU/LV, in terms of progression-free survival (PFS), overall survival (OS), and response rate (Table 1)[11,12]. The prospectively planned,

Table 2 Comparison of treatment safety (Grade 3/4 events) as a monotherapy

Clinical trial	Treatments	Diarrhea	Neutropenia	Stomatitis	HFS
Van Cutsem *et al*[12] (2001)	Capecitabine *vs* 5-FU/LV	10.7% *vs* 10.4%	2.0% *vs* 19.8%[a]	1.3% *vs* 13.3%[a]	16.2% *vs* 0.3%[a]
Hoff *et al*[11] (2001)	Capecitabine *vs* 5-FU/LV	15.4% *vs* 13.9%	2.6% *vs* 25.9%[a]	3.0% *vs* 16.0%[a]	18.1% *vs* 0.7%[a]
Cassidy *et al*[14] (2002)	Capecitabine *vs* 5-FU/LV	13.1% *vs* 12.2%	2.3% *vs* 22.8%[a]	2.0% *vs* 14.7%[a]	17.1% *vs* 1%[a]

[a]$P < 0.05$ *vs* capecitabine group; HFS: Hand-foot syndrome; LV: Leucovorin.

integrated analysis confirmed comparable time to progression (TTP) and OS and further demonstrated the superiority of capecitabine, compared to 5-FU/LV, in overall response rate (ORR) (26% *vs* 17%, $P < 0.002$)[13]. The integrated analysis also demonstrated that capecitabine offered an improved safety profile over 5-FU/LV treatment, with significantly lower incidences of diarrhea, stomatitis, nausea, alopecia, and grade 3-4 neutropenia (Table 2). In comparison, the only adverse event (AE) that occurred significantly ($P < 0.001$) more frequently with capecitabine than with 5-FU/LV was hand-foot syndrome (HFS)[14]. Furthermore, the integrated analysis demonstrated that the 5-FU group suffered from a significantly higher number of dose reductions due to AEs (33.9% *vs* 42.2%, $P = 0.0037$) and a significant increase in the number of hospitalizations (11.6% *vs* 18.0%, $P < 0.005$). After a second dose reduction, those patients treated with 5-FU exhibited a slightly increased (not statistically significant) risk of disease progression (HR = 1.30 *vs* 1.06).

In this analysis, due to the higher incidence of severe events associated with capecitabine and renal insufficiency (clearance 30-50 mL/min), it was recommended to reduce the initial starting dose of capecitabine to 75% in moderate renal insufficiency patients, and it was contraindicated in patients with severe renal insufficiency. Therefore, for patients with moderate renal insufficiency, the most suitable treatment was concluded to be capecitabine due to its maintained efficacy at reduced doses, whereas under the same conditions, the efficacy of 5-FU was shown to be lower. It is important to note that for patients with moderate hepatic insufficiency that was secondary to metastasis and who did not present with a high accumulation of pre-metabolites, a dose reduction to avoid capecitabine-associated toxicity was not required[15].

In addition to offering improved efficacy for patients with both renal insufficiency and hepatic insufficiency, capecitabine monotherapy has also been assessed in elderly patients older than 70 years. In this group, capecitabine was found to exhibit a 67% disease control rate (DCR), an 11-mo median OS, and a 7-mo TTP, as well as a low incidence (12%) of grade 3-4 AEs[16]. Thus, the study concluded that the reduction in the number of hospital visits made capecitabine an effective and well-tolerated therapy for elderly patients who were ineligible for combination chemotherapy.

The development of 5-FU/LV continuous infusion therapy, in conjunction with oxaliplatin and irinotecan treatment, has led to a lack of comparative studies that have directly compared capecitabine and continuously infused 5-FU/LV. However, studies have been conducted that compared capecitabine and 5-FU/LV, albeit as a combination of capecitabine and oxaliplatin, or irinotecan. Furthermore, since the introduction of biological drug therapies, several studies have further examined capecitabine's efficacy and safety in elderly populations.

In a multicenter, phase Ⅱ clinical trial by Feliu *et al*[17] capecitabine was used in combination with the biological agent bevacizumab as a first-line treatment in elderly mCRC patients. These authors demonstrated a 34% ORR, a 71% DCR, 10.8-mo PFS and 18-mo OS, all of which were comparable to capecitabine as a monotherapy. Interestingly, the most common grade 3-4 events were HFS (19%), diarrhea (9%) and deep vein thrombosis (7%).

Recently, the randomized, phase Ⅲ AVEX clinical trial results were presented at the 2013 ASCO meeting[18]. This study compared capecitabine alone to capecitabine and bevacizumab combination treatment in ≥ 70-year-old patients, to determine PFS. The study found a significant improvement in PFS for the combination therapy (9.1 mo for the bevacizumab arm *vs* 5.1 mo for capecitabine alone, HR = 0.53, $P < 0.0001$), with benefits observed in all of the subgroups. In turn, there was significant improvement in overall response rate with bevacizumab (19.3% *vs* 10%, $P = 0.042$). However, the difference in OS for bevacizumab did not reach statistical significance (20.7 mo *vs* 16.8 mo, HR = 0.79, $P = 0.182$), and the safety profile was similar to that reported in other studies.

The combination of capecitabine with the biological agent cetuximab has been viewed as an alternative to capecitabine/bevacizumab in patients with *wtKRAS* and other risk factors preventing the use of bevacizumab. According to data presented by the Spanish TTD Group study[19], the initial dose of capecitabine used (1250 mg/m^2 twice daily for 14 d), in combination with cetuximab, produced a high incidence of paronychia and a grade 3-4 acne-like rash, requiring a dose reduction of capecitabine to 1000 mg/m^2 twice daily, which decreased the paronychia incidence but not the acne-like rash incidence. Nevertheless, ORR (48%) and PFS (8.4 mo) performance data for *wtKRAS* patients demonstrated significant improvement over those shown by capecitabine when used as a monotherapy in unselected patients.

Altogether, these studies have reinforced the need to observe toxicity closely to manage dose adjustments, if required, for elderly patients and patients with hepatic or

renal insufficiency to maintain suitable tolerability.

THE COMBINATION OF CAPECITABINE WITH OXALIPLATIN

Several randomized, phase Ⅲ studies have compared the efficacy and safety of oral or *iv* fluoropyrimidines, in combination with oxaliplatin, as first-line treatments for mCRC. The aforementioned XELOX scheme has been compared directly with FUOX (48-h continuous infusion of 2250 mg/m^2 5-FU on days 1, 8, 15, 22, 29 and 36 and 85 mg/m^2 oxaliplatin on days 1, 15, and 29; 6-wk regimen cycle)[20], FOLFOX-4 (2-h infusion of 85 mg/m^2 oxaliplatin; 2-h infusion of 200 mg/m^2 LV, followed by bolus of 400 mg/m^2 5-FU, followed by 22-h continuous infusion of 600 mg/m^2 5-FU; 2-wk regimen cycle)[21], and FOLFOX-6 (described earlier)[9].

The Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD) demonstrated comparable efficacy of XELOX compared to FUOX in TTP (8.9 mo *vs* 9.5 mo, $P = 0.153$), median OS (18.1 mo *vs* 20.8 mo, $P = 0.145$) and ORR (37% *vs* 46%, $P = 0.539$). In addition, the safety profiles were also similar, with both treatment arms exhibiting a 27% treatment discontinuation rate due to toxicity; however, despite this similarity, grade 3-4 diarrhea was significantly more common in the FUOX arm (14% *vs* 24%, $P = 0.027$)[20].

A French study that compared XELOX to FOLFOX-6[9] also met the primary endpoint of non-inferiority in ORR (42% *vs* 46%). Furthermore, no significant differences were observed in either the PFS (8.8 mo *vs* 9.3 mo) or OS (19.9 mo *vs* 20.5 mo) efficacy parameters. A higher incidence of grade 3-4 neuropathy (11% *vs* 26%, $P < 0.001$) was observed when using the highest oxaliplatin dose for FOLFOX-6, and in addition, a significantly higher incidence of grade 3-4 neutropenia was also observed for FOLFOX-6 (5% *vs* 47%, $P < 0.001$). In contrast, diarrhea (14% *vs* 7%, $P = 0.0034$) was found to occur with a significantly higher frequency with XELOX.

Other combinations have been evaluated by German (CAPOX)[22] and Italian (OXXEL)[23] groups. In the first study, the CAPOX regimen (1000 mg/m^2 oral capecitabine twice daily for 14 d; 70 mg/m^2 oxaliplatin on days 1 and 8; 3-wk regimen cycle) was compared with FUFOX (50 mg/m^2 oxaliplatin; 500 mg/m^2 LV; 22-h continuous infusion of 2000 mg/m^2 5-FU on days 1, 8, 15, and 22; 5-wk regimen cycle), and CAPOX failed to meet the primary endpoint of non-inferiority in PFS (7.1 mo *vs* 8.0 mo, HR = 1.17, $P = 0.117$). In addition, despite the ORR and OS being lower with CAPOX, the difference was not statistically significant. The safety profiles of the two regimens were similar; however, a significantly higher incidence of grade 2-3 HFS was noted in the CAPOX arm (10% *vs* 4%, $P = 0.028$)[22].

The second study compared an OXXEL regimen (100 mg/m^2 oxaliplatin on day 1; 1000 mg/m^2 oral capecitabine twice daily for 11 d; 2-wk regimen cycle) with an OXAFAFU regimen (85 mg/m^2 oxaliplatin on day 1; 250 mg/m^2 LV day 1; 850 mg/m^2 5-FU bolus on day 2; 2-wk regimen cycle) and found similar efficacy results for ORR (34% *vs* 33%, $P = 0.999$), PFS (6.6 mo *vs* 6.5 mo, $P = 0.354$), and OS (16.0 mo *vs* 17.1 mo, $P = 0.883$). A more acceptable safety profile was observed with the OXXEL regimen (32% *vs* 43% grade 3-4 events)[23].

The largest study that included oxaliplatin was the NO16966 study. Its initial non-inferiority design between XELOX and FOLFOX-4 was subsequently redesigned to be a 2 × 2 randomization study with the addition of bevacizumab/placebo. By the end of recruitment, more than 2000 patients were enrolled in the study. The first co-primary objective of non-inferiority of XELOX (versus FOLFOX-4) in PFS was reached (8.0 mo *vs* 8.5 mo, HR = 1.04) with no observable differences in OS or ORR[21]. The second co-primary objective, evaluating the impact on PFS of adding bevacizumab, showed a significant increase in PFS in the bevacizumab arm (*vs* placebo) (9.4 mo *vs* 8.0 mo, HR = 0.83, $P = 0.0023$)[24]. This benefit was not reflected in OS or ORR, most likely due to the high rate of treatment discontinuation before progression. Regarding the safety profile, the group treated with FOLFOX-4 had a higher incidence of grade 3-4 neutropenia, febrile neutropenia and thromboembolic events, whereas XELOX treatment resulted in a higher incidence of grade 3-4 diarrhea and HFS. Importantly, the toxicity profile was not affected by the addition of bevacizumab.

In the first phase of the randomized, phase Ⅱ TREE study (TREE-1), oxaliplatin was combined with different forms of fluoropyrimidine administration to form three groups: FOLFOX-6, bFOL (85 mg/m^2 oxaliplatin on days 1 and 15; 20 mg/m^2 bolus LV; 500 mg/m^2 bolus 5-FU on days 1, 8, and 15; 4-wk regimen cycle), and XELOX (capecitabine with oxaliplatin)[25]. A comparison of these groups revealed an insignificantly higher ORR, TTP, and OS with FOLFOX-6 and increased toxicity with XELOX (greatest number of interruptions due to grade 3/4 diarrhea). In TREE-2, bevacizumab was included, which resulted in improved efficacy parameters for all of the treatment groups. XELOX toxicity was reduced (equivalent to all other schemes) after dose adjustment. Detailed results for the efficacy and safety of these studies are presented in Tables 3 and 4, respectively.

These randomized studies were evaluated in two meta-analyses[26,27]. Response rates to 5-FU in combination with oxaliplatin were higher (significant only in the first study: OR 0.74, $P = 0.007$); however, this outcome did not result in improved survival parameters. Regarding the toxicity profile, the first meta-analysis[26] did not offer conclusive findings due to the heterogeneity of the treatment groups (mainly with 5-FU). In the other, more recent study[27]. significant differences were observed in the frequency of grade 4 neutropenia and diarrhea and toxicity in the 5-FU group ($P = 0.078$). In both studies, the largest significant incidence of grade 3 HFS occurred with capecitabine.

Favorable efficacy results have been reported for

Table 3 Comparison of treatment efficacy in combination with oxaliplatin

Clinical trial	Type	Treatment	ORR	PFS (mo)	OS (mo)
Díaz-Rubio *et al*[20] (2007)	Phase Ⅲ	XELOX *vs* FUOX	37% *vs* 46% (P = 0.154)	8.9 *vs* 9.5 (HR = 1.18, P = 0.153)	18.1 *vs* 20.8 (HR 1.22, P = 0.145)
Cassidy *et al*[45] (2008)	Phase Ⅲ	XELOX *vs* FOLFOX-4 +/- Bev	47% *vs* 48% (OR 0.94)	8 *vs* 8.5 (HR = 1.04)[1]	19.8 *vs* 19.6 (HR = 0.99)
Ducreux *et al*[42] (2011)	Phase Ⅲ	XELOX *vs* FOLFOX-6	42% *vs* 46%	8.8 *vs* 9.3 (HR = 1)	19.9 *vs* 20.5 (HR = 1.02)
Porschen *et al*[22] (2007)	Phase Ⅲ	CAPOX *vs* FUFOX	48% *vs* 54% (P = 0.7)	7.1 *vs* 8.0 (HR = 1.17, P = 0.117)	16.8 *vs* 18.8 (HR = 1.12, P = 0.26)
Comella *et al*[23] (2009)	Phase Ⅲ	OXXEL *vs* OXAFAFU	34% *vs* 33% (P = 0.999)	6.6 *vs* 6.5 (HR = 1.12, P = 0.354)	16.0 *vs* 17.1 (HR = 1.01, P = 0.883)
Hochster *et al*[25] (2008)	Phase Ⅱ	XELOX *vs* FOLFOX-6 *vs* bFOL+ Bev	27% *vs* 41% *vs* 20%; 46% *vs* 52% *vs* 39%	5.9 *vs* 8.7 *vs* 6.9; 10.3 *vs* 9.9 *vs* 8.3	17.2 *vs* 19.2 *vs* 17.9; 24.6 *vs* 26.1 *vs* 20.4

Treatments: XELOX: Capecitabine 1000 mg/m^2 every 12 h (days 1-14) + 130 mg/m^2 oxaliplatin (day 1), 3-wk regimen cycle; FUOX: 2250 mg/m^2 5-FU continuous infusion for 48 h (days 1, 8, 15, 22, 29 and 36) + 85 mg/m^2 oxaliplatin (days 1, 15 and 29) 6-wk regimen cycle; FOLFOX-4: 400 mg/m^2 5-FU bolus + 200 mg/m^2 LV + 600 mg/m^2 continuous infusion 5-FU for 22 h (days 1 and 2) + oxaliplatin 85 mg/m^2 (day 1) 2-wk regimen cycle, FOLFOX-6: 400 mg/m^2 5-FU bolus + 400 mg/m^2 LV + 2400 mg/m^2 46 h 5-FU continuous infusion + 100 mg/m^2 oxaliplatin (day 1), 2-wk regimen cycle); CAPOX: 1000 mg/m^2 capecitabine every 12 h (days 1-14) + 70 mg/m^2 oxaliplatin (days 1 and 8, 3-wk regimen cycle; FUFOX: 500 mg/m^2 LV + 50 mg/m^2 oxaliplatin + 2000 mg/m^2 5-FU continuous infusion for 22 h (days 1, 8, 15 and 22), 5-wk regimen cycle; OXXEL: 1000 mg/m^2 capecitabine every 12 h (days 1-11) + 100 mg/m^2 oxaliplatin (day 1), 2-wk regimen cycle; OXAFAFU: 250 mg/m^2 LV + 85 mg/m^2 oxaliplatin (day 1) + 850 mg/m^2 5-FU bolus (day 2), 2-wk regimen cycle; bFOL: 20 mg/m^2 LV + 85 mg/m^2 oxaliplatin (days 1 and 15) + 500 mg/m^2 5-FU bolus (days 1 and 8-15), 4-wk regimen cycle. ORR: Overall response rate; PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; Bev: Bevacizumab. [1]Significant PFS difference between XELOX + bevacizumab (HR = 0.77, P = 0.0026).

Table 4 Comparison of treatment safety (Grade 3/4 events) in combination with oxaliplatin

Clinical trial	Treatments	Diarrhea	Mucositis/ stomatitis	Neutropenia	HFS	Vomiting (%)
Díaz-Rubio *et al*[20] (2007)	XELOX *vs* FUOX	14% *vs* 24%[a]	2% *vs* 4%	7% *vs* 11%	2% *vs* 1%	5% *vs* 8%
Cassidy *et al*[21] (2008)	XELOX *vs* FOLFOX-4 +/- Bev	19% *vs* 11%	1% *vs* 2%	7% *vs* 44%	6% *vs* 1%	5% *vs* 4%
Ducreux *et al*[9] (2011)	XELOX *vs* FOLFOX-6	14% *vs* 7%[a]	0% *vs* 1%	5% *vs* 47%[a]	3% *vs* 1%	2% *vs* 5%
Porschen *et al*[22] (2007)	CAPOX *vs* FUFOX	15% *vs* 14%	1% *vs* 3%	-	10% *vs* 4%[c]	6% *vs* 6%
Comella *et al*[23] (2009)	OXXEL *vs* OXAFAFU	13% *vs* 8%	2% *vs* 2%	10% *vs* 27%[e]	4% *vs* 1%	3% *vs* 8%[e]
Hochster *et al*[25] (2008)	XELOX *vs* FOLFOX-6 *vs* bFOL + Bev[1]	31% *vs* 31% *vs* 26% 19% *vs* 11% *vs* 26%	-	15% *vs* 53% *vs* 18% 10% *vs* 49% *vs* 19%	19% *vs* 8% *vs* 2% 10% *vs* 0% *vs* 0%	38% *vs* 31% *vs* 24% 21% *vs* 7% *vs* 24%

[1]Reduced XELOX dose (850 mg/m^2 capecitabine). Treatments: XELOX: Capecitabine 1000 mg/m^2 every 12 h (days 1-14) + 130 mg/m^2 oxaliplatin (day 1), 3-wk regimen cycle; FUOX: 2250 mg/m^2 5-FU continuous infusion for 48 h (days 1, 8, 15, 22, 29 and 36) + 85 mg/m^2 oxaliplatin (days 1, 15 and 29) 6-wk regimen cycle; FOLFOX-4: 400 mg/m^2 5-FU bolus + 200 mg/m^2 LV + 600 mg/m^2 continuous infusion 5-FU for 22 h (days 1 and 2) + oxaliplatin 85 mg/m^2 (day 1) 2-wk regimen cycle, FOLFOX-6: 400 mg/m^2 5-FU bolus + 400 mg/m^2 LV + 2400 mg/m^2 46 h 5-FU continuous infusion + 100 mg/m^2 oxaliplatin (day 1), 2-wk regimen cycle); CAPOX: 1000 mg/m^2 capecitabine every 12 h (days 1-14) + 70 mg/m^2 oxaliplatin (days 1 and 8, 3-wk regimen cycle; FUFOX: 500 mg/m^2 LV + 50 mg/m^2 oxaliplatin + 2000 mg/m^2 5-FU continuous infusion for 22 h (days 1, 8, 15 and 22), 5-wk regimen cycle; OXXEL: 1000 mg/m^2 capecitabine every 12 h (days 1-11) + 100 mg/m^2 oxaliplatin (day 1), 2-wk regimen cycle; OXAFAFU: 250 mg/m^2 LV + 85 mg/m^2 oxaliplatin (day 1) + 850 mg/m^2 5-FU bolus (day 2), 2-wk regimen cycle; bFOL: 20 mg/m^2 LV + 85 mg/m^2 oxaliplatin (days 1 and 15) + 500 mg/m^2 5-FU bolus (days 1 and 8-15), 4-wk regimen cycle. Bev: Bevacizumab; HFS: Hand-foot syndrome. [a]P < 0.05 *vs* XELOX; [c]P < 0.05 *vs* CAPOX; [e]P < 0.05 *vs* OXXEL.

XELOX as a first-line mCRC treatment in the elderly in several studies[28,29]. The first, a phase Ⅱ study, enrolled 50 patients with a mean age of 76 years and recorded an ORR of 36%, a DCR of 72%, TTP of 5.8 mo, and OS of 13.2 mo. The grade 3-4 toxicity profile was lower than that in other studies (28% of patients exhibited AEs, mainly gastrointestinal and asthenia).

A sub-analysis of the phase Ⅲ TTD study[20] was conducted by Sastre *et al*[30] who compared the efficacy and safety of XELOX and FUOX regimens in > 70- and < 70-year-old patient subgroups. No significant differences were observed in terms of efficacy between the two age groups. In the group treated with FUOX, the number of overall treatment delays was greater, compared to both XELOX subgroups. Furthermore, among the FUOX-treated patients, those aged > 70 years had higher dose reductions, whereas with the XELOX regimen, there were no differences between the age subgroups. The toxicity profile was favorable in both groups, except for a significant increase in grade 3-4 diarrhea in the > 70-year-old XELOX subgroup (25% *vs* 8%, P = 0.005).

A response rate of 41%, median PFS of 8.5 mo, and median OS of 14.4 mo, were reported in an Italian study of elderly patients (mean age of 76 years)[29]. Patients older than 75 years demonstrated a higher ORR compared to the younger patients; however, no further differences in survival were noted.

As amendments to the NO16966 and TREE-2 study protocols, the BEAT study[31] included the addition of bevacizumab to various chemotherapy regimens: XE-

LOX, FOLFOX-6 or FOLFIRI (180 mg/m^2 irinotecan, day 1; 200 mg/m^2 2-h infusion LV, day 1; 400 mg/m^2 IV bolus 5-FU, day 1; 46-h continuous infusion of 2400 mg/m^2 5-FU; 14-d regimen cycle). The efficacy (TTP, PFS and OS) and safety profiles demonstrated no significant differences between the groups.

The COIN study[32] was performed to evaluate the efficacy and toxicity of adding cetuximab to oxaliplatin combinations. The initial objective was to demonstrate a benefit to OS in the experimental cetuximab arm; however, after the results found poorer survival with anti-EGFR in the mutated KRAS population, the new goal became to determine a benefit to OS with cetuximab in *wtKRAS* patients. In this population, the highest response rate (64% *vs* 57%, OR 1.35, $P = 0.049$) did not translate into PFS or OS benefit. The toxicity profile (diarrhea and cutaneous toxicity) of the XELOX combination was high, requiring a dose reduction of capecitabine in the experimental arm (from 1000 mg/m^2 to 850 mg/m^2 twice daily). The only subgroup that was treated with cetuximab that also showed benefits in PFS was that with *wtKRAS* and involvement of $\leqslant 1$ organs and that was treated with 5-FU (HR = 0.55, $P = 0.011$). The lack of a benefit of cetuximab in combination with oxaliplatin appeared to be connected to the toxicity associated with capecitabine (more than 2/3 of the patients were treated with XELOX). These data did not support the recommendation of this combination.

COMBINATION OF CAPECITABINE WITH IRINOTECAN

The development of the capecitabine and irinotecan combination was much slower and more complex compared to the XELOX regimen due to increased toxicity.

In 2005, a phase Ⅰ/Ⅱ study established a recommended dose for the combination of 250 mg/m^2 irinotecan (day 1) + 1000 mg/m^2 capecitabine twice daily (days 1-14), with a regimen cycle of 21 d[33]. These doses were those used in the EORTC 40015 study[34], which compared the FOLFIRI and CAPIRI (250 mg/m^2 *iv* irinotecan, days 1 and 22; 1000 mg/m^2 oral capecitabine, twice daily on days 1-15 and 22-36) regimens in combination with celecoxib or placebo (800 mg, 2 × 200 mg twice daily). The number of grade 3-4 AEs was higher with CAPIRI, with febrile neutropenia being the most statistically significant AE reported ($P < 0.001$). After 7 treatment-related deaths (6 of them with CAPIRI), the study was prematurely terminated.

This combination has been studied using various forms of administration. Garcia-Alfonso *et al*[35] conducted a study using the XELIRI regimen (175 mg/m^2 irinotecan, day 1; 1000 mg/m^2 capecitabine, twice daily, days 2-8 every 2 wk (reduced to 140 mg/m^2 and 750 mg/m^2 in patients older than 65 years old, respectively), which exhibited an ORR of 32%, DCR of 66%, PFS of 9.0 mo, and OS of 19.2 mo. The toxicity profile was favorable, with diarrhea (15%) and grade 3 asthenia (13%) being the most frequent adverse events reported.

This regimen was subsequently combined with bevacizumab (5 mg/kg, day 1) in a subsequent phase Ⅱ study, which demonstrated an increased benefit (67.4% ORR, DCR 93%, PFS 12.3 mo and OS 23.7 mo) while maintaining a similar toxicity profile to the previous study[36].

The next improvements involved a tri-weekly schedule of 800 mg/m^2 capecitabine twice daily (days 1-14) with irinotecan 200 mg/m^2 (day 1), which demonstrated a suitable safety profile and superior efficacy when given in combination with either cetuximab[37] or bevacizumab[38].

In light of the TREE study, the BICC-C study[39] was developed as a phase Ⅲ, randomized trial that compared irinotecan in combination with different forms of fluoropyrimidine administration. In terms of efficacy, FOLFIRI exhibited the most significant benefit in PFS, compared to mIFL (7.6 mo *vs* 5.9 mo, $P = 0.004$) and CapeIRI (7.6 mo *vs* 5.8 mo, $P = 0.015$); however, it did not exhibit any significant improvement in OS or ORR. Regarding safety profiles, grade 3-4 toxicity was higher with CapeIRI compared to FOLFIRI (nausea/vomiting 34% *vs* 17.6%; diarrhea 47.5% *vs* 13.9%; dehydration 19.1% *vs* 5.8%), requiring treatment interruption in more patients (25.5% *vs* 14.6% for FOLFIRI; and 13.5% for mIFL). Following an amendment to the protocol to add bevacizumab (Bev. 5 mg/kg), the 2nd phase began, with the CapeIRI arm discontinued due to toxicity. In this phase, the FOLFIRI-Bev combination showed a significant OS benefit over mIFL-Bev (28 mo *vs* 19.2 mo, $P = 0.037$).

Since the BICC-C study, successive randomized phase Ⅱ and Ⅲ studies have been performed to compare both schemes with the addition of bevacizumab, and similar efficacy outcomes have been observed in all of them, albeit with differences in the reported safety profiles.

The first of these-a phase Ⅱ, randomized study between CAPIRI-Bev and FOLFIRI-Bev[40]-found no significant differences in PFS, OS or response rate. Despite these outcomes, the incidences of diarrhea (15.8% *vs* 9.2%, $P = 0.003$) and grade 3-4 HFS (4.2% *vs* 1.2%, $P = 0.03$) were significantly higher with CAPIRI-Bev. This fact resulted in greater numbers of delays (15.6% *vs* 9%, $P = 0.05$), dose reductions (10.9% *vs* 4.3%, $P < 0.001$), and interruptions in treatment (10.2% *vs* 4.2%, $P = 0.04$).

In contrast, a phase Ⅲ and phase Ⅱ trial demonstrated a more favorable toxicity profile with XELIRI, with no detriment to the efficacy. The phase Ⅲ study demonstrated similar efficacy in the XELIRI-Bev arm versus FOLFIRI-Bev, with a generally lower incidence of grade 3-4 events and no significant differences in toxicity profiles between the two arms[41]. This favorable profile reappeared in a phase Ⅱ study with a design (except for an initial dose reduction of CPT-11 and a capecitabine adjustment according to age) similar to that of the previous study, but with the continuation of bevacizumab until progression[42]. The response and survival data were similar, while the incidence of toxicity with XELIRI was lower than in other studies (diarrhea 12% *vs* 7%, and thromboembolic events 3% *vs* 8%). However, more patients required interruption due to toxicity (17% *vs* 7%).

Table 5 Comparison of treatment efficacy in combination with irinotecan

Clinical trial	Type	Treatment	ORR	PFS (mo)	OS (mo)
Fuchs *et al*[39] (2007)	Phase Ⅲ	CapeIRI[1] *vs* FOLFIRI *vs* mIFL	38.6% *vs* 47.2% *vs* 43.3%	5.8 *vs* 7.6 (1) *vs* 5.9 (2)	18.9 *vs* 23.1 (3) *vs* 17.6
Köhne *et al*[34] (2008)[2]	Phase Ⅲ	CAPIRI *vs* FOLFIRI-2		5.9 *vs* 9.6	14.75 *vs* 19.9
		+ Celecoxib	22% *vs* 32%		
		- Celecoxib	48% *vs* 45%		
Souglakos *et al*[40] (2012)	Phase Ⅱ	CAPIRI + Bev *vs* FOLFIRI-2 + Bev	39.8% *vs* 45.5% (P = 0.32)	8.9 *vs* 10.0 (P = 0.64)	27.5 *vs* 25.7 (P = 0.55)
Pectasides *et al*[41] (2012)	Phase Ⅲ	XELIRI + Bev *vs* FOLFIRI + Bev	38.5% *vs* 40.1% (P = 0.81)	10.2 *vs* 10.8 (P = 0.74)	20.0 *vs* 25.3 (P = 0.099)
Ducreux *et al*[42] (2013)	Phase Ⅱ	XELIRI-2+ Bev *vs* FOLFIRI + Bev	62% *vs* 63%	9 *vs* 9	23 *vs* 23

[1]Arm excluded after protocol amendment for toxicity; [2]Premature termination due to toxicity (inconclusive results). Treatments: CapeIRI (CAPIRI): 250 mg/m^2 Irinotecan (day 1) + 1000 mg/m^2 capecitabine (days 1-14), 3-wk regimen cycle; FOLFIRI: 180 mg/m^2 irinotecan + 400 mg/m^2 LV + 400 mg/m^2 5-FU bolus + 2400 mg/m^2 5-FU 46-h continuous infusion, 2-wk regimen cycle; mIFL: 125 mg/m^2 irinotecan + 20 mg/m^2 LV + 500 mg/m^2 5-FU bolus (days 1 and 8), 3-wk regimen cycle; FOLFIRI-2: 180 mg/m^2 irinotecan (days 1, 15, 22) + 200 mg/m^2 LV (days 1, 2, 15, 16, 29, and 30)+ 400 mg/m^2 bolus 5-FU, 600 mg/m^2 22-h continuous infusion 5-FU (1, 2, 15, 16, 29 and 30); XELIRI: 240 mg/m^2 irinotecan + 1000 mg/m^2 capecitabine (days 1-14), 3-wk treatment regimen; XELIRI-2: 200 mg/m^2 irinotecan + 1,000 mg/m^2 capecitabine (days 1-14), 3-wk treatment regimen. ORR: Overall response rate; PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; Bev: Bevacizumab. (1) CapeIRI *vs* FOLFIRI (P = 0.015); (2) CapeIRI *vs* mIFL (P = 0.46); and (3) CapeIRI *vs* FOLFIRI (P = 0.27).

Table 6 Comparison of treatment safety (Grade 3/4 events) in combination with irinotecan

Clinical trial	Treatments	Diarrhea	Vomiting	Neutropenia	HFS
Fuchs *et al*[39] (2007)	[1]CapeIRI *vs* FOLFIRI *vs* mIFL	47.5% *vs* 13.9% *vs* 19.0%	18.4% *vs* 8.8% *vs* 7.3%	31.9% *vs* 43.1% *vs* 40.9%	9.9% *vs* 0% *vs* 0%
Köhne *et al*[34] (2008)[2]	CAPIRI *vs* FOLFIRI-2				
	+ Celecoxib	39% *vs* 17%	9% *vs* 6%	13% *vs* 11%	< 1% *vs* 0%
	- Celecoxib	35% *vs* 10%	5% *vs* 5%	15% *vs* 19%	< 1% *vs* 0%
Souglakos *et al*[40] (2012)	CAPIRI + Bev *vs* FOLFIRI-2 + Bev	15.8% *vs* 9.2%[a]	-	17.9% *vs* 24.5%	4.2% *vs* 1.2%[a]
Pectasides *et al*[41] (2012)	XELIRI + Bev *vs* FOLFIRI + Bev	19% *vs* 11%	5% *vs* 0%[c]	13% *vs* 22%	-
Ducreux *et al*[42] (2013)	XELIRI-2+ Bev *vs* FOLFIRI + Bev	12% *vs* 5%	7% *vs* 7%	18% *vs* 26%	6% *vs* 1%

[1]Arm excluded after protocol amendment for toxicity; [2]Premature termination due to toxicity (inconclusive results). Treatments: CapeIRI (CAPIRI): 250 mg/m^2 Irinotecan (day 1) + 1000 mg/m^2 capecitabine (days 1-14), 3-wk regimen cycle; FOLFIRI: 180 mg/m^2 irinotecan + 400 mg/m^2 LV + 400 mg/m^2 5-FU bolus + 2400 mg/m^2 5-FU 46-h continuous infusion, 2-wk regimen cycle; mIFL: 125 mg/m^2 irinotecan + 20 mg/m^2 LV + 500 mg/m^2 5-FU bolus (days 1 and 8), 3-wk regimen cycle; FOLFIRI-2: 180 mg/m^2 irinotecan (days 1, 15, 22) + 200 mg/m^2 LV (days 1, 2, 15, 16, 29, and 30)+ 400 mg/m^2 bolus 5-FU, 600 mg/m^2 22-h continuous infusion 5-FU (1, 2, 15, 16, 29 and 30); XELIRI: 240 mg/m^2 irinotecan + 1000 mg/m^2 capecitabine (days 1-14), 3-wk treatment regimen; XELIRI-2: 200 mg/m^2 irinotecan + 1000 mg/m^2 capecitabine (days 1-14), 3-wk treatment regimen. Bev: Bevacizumab; HFS: Hand-foot syndrome; [a]P < 0.05 *vs* CAPIRI + Bev; [c]P < 0.05 *vs* XELIRI + Bev.

From these data, it can be concluded that the XELIRI combination might be an option, provided that there is a dose adjustment and proper management of side effects.

Tables 5 and 6 show the efficacy and safety data in combination with irinotecan, respectively.

IS ORAL TREATMENT ECONOMICALLY VIABLE?

The phase Ⅲ European study of the efficacy and safety of monotherapy[12] included a cost and resource use analysis[43]. In this analysis, the authors found that by using capecitabine, scheduled visits to the hospital were reduced by more than 70%, while unscheduled consultations increased slightly in this group. The number and duration of hospitalizations and the incidences of infections/sepsis, neutropenia and stomatitis were lower, resulting in a significant reduction in pharmaceutical expenditures.

Similar pharmacoeconomic results were obtained in a data analysis from the X-ACT study[44] comparing capecitabine and 5-FU/LV (based on the Mayo Clinic regimen). The better efficacy and safety profile of oral capecitabine treatment was found to be more expensive in terms of drug acquisition costs; however, this higher cost was offset by the reduced costs for overall chemotherapy (57%), fewer hospital admissions and shorter stays (15%)[45].

The results of a retrospective analysis of patients receiving capecitabine or 5-FU/LV monotherapy or capecitabine/5-FU with oxaliplatin revealed that treatment with capecitabine monotherapy represented the largest, but non-significant, cost reduction[46]. These savings were found to be due to fewer secondary treatment complications (and therefore fewer visits and hospital admissions), which accommodated the higher direct drug acquisition costs. Interestingly, when combined with oxaliplatin, no differences were observed between capecitabine and 5-FU regarding treatment-related costs or associated complications.

A comparative analysis of oral monotherapy treatment regimens (capecitabine or tegafur with uracil in combination with LV), compared to the Mayo clinic regimen, again showed that the most significant cost in oral therapy (drug acquisition) was offset by a reduction in administrative costs[47].

Despite the weight of evidence supporting the cost-benefits of oral therapy, these benefits do not seem to translate to all geographical regions. For example, a recent Swedish study compared the Nordic FLIRI and FLOX regimens with XELIRI and XELOX, and it found that despite the higher direct drug acquisition costs, the overall costs were similar[48]. Furthermore, a recent Japanese study analyzed data from the NO16966 and NO16967 studies and found that XELOX demonstrated a better cost-effective profile than FOLFOX-4 both as first- and second-line therapy[49].

Therefore, altogether, these studies suggest a country-specific pharmacoeconomic benefit of oral-based therapy. The studies clearly emphasize the necessity of performing individual cost-benefit analyses before implementing economically driven treatment modifications.

CONCLUSION

In recent years, the survival of patients with mCRC has improved significantly with the addition of newer and more effective drugs. Nevertheless, fluoropyrimidines still play a fundamental role. The opinion and preference of the patient in the context of treatment for palliative means constitute a priority. The preference for the convenience of oral treatment is clear, provided that efficacy and tolerable toxicity are not undermined.

The progressive increase in life expectancy in the population has been related to a greater number of patients reaching old age in a good general condition and, in turn, the incidence of cancer in this population increasing. For safety and convenience, capecitabine is a good choice in this group of older patients. Sufficient knowledge of the AE profile and dose management for age and renal/hepatic function are essential to ensure tolerability and adherence to treatment.

Capecitabine has proved to be an effective substitute for 5-FU as monotherapy or in combination with oxaliplatin and irinotecan. However, in combination with the latter drug, controversy persists regarding its safety profile. Nevertheless, progress continues, with recent studies indicating that a toxicity reduction could be achieved, while maintaining efficiency, with dose adjustment and appropriate management of AEs by the physician.

Contrary to the initial idea of additional costs generated by oral treatment, pharmacoeconomic analyses have shown that, within the overall perspective of costs (treatment, management, and complications), orally administered treatment appears to be more economical than, or at least comparable to, *iv* treatments.

Thus, to conclude from the results reported herein, capecitabine appears to be an effective, safe, convenient, and economically viable alternative to 5-FU as a first-line treatment for mCRC.

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