

## Colorectal Cancer: Focus on Capecitabine

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**Abstract:** Capecitabine is an oral pro-drug of 5-fluorouracil (5FU) that has demonstrated an efficacy at least equivalent to standard leucovorin (LV)-modulated 5FU I.V. bolus regimen in the management of metastatic colorectal cancer (MCRC) patients as well as in the adjuvant setting. Despite a mild increase of some side effects, capecitabine is usually better tolerated than 5FU/LV, and could be preferable in the treatment of elderly patients. Moreover, usually the patients compliance with an oral treatment is better than with a regimen requiring the placement of a central venous catheter and infusional devices. The combination of capecitabine with oxaliplatin (XELOX regimen) was shown to be as effective as the combination of 5FU/LV with oxaliplatin (FOLFOX4 regimen) in MCRC. The XELOX regimen represents now a new standard of care for MCRC patients, and it will be probably considered in the next future an “user-friendly” alternative to the FOLFOX4 also in resected patients. The addition of bevacizumab to the XELOX regimen was demonstrated to further prolong the progression-free survival of metastatic patients, and is anticipated to reduce the risk of recurrence in resected colon cancer. Despite a higher acquisition cost than 5FU/LV, capecitabine is also cost-effective, because of the reduced costs for drug administration and management of adverse events.

**Keywords:** colorectal cancer, capecitabine

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## Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer death in the Western world.<sup>1</sup> CRC patients are frequently diagnosed in an advanced stage, and the surgical resection of the primary tumor does not always translate into cure. Indeed, 5-year overall survival (OS) after surgery is about 67% for patients with lymph nodes spread (stage III), and is usually less than 10% for those with distant metastases. Therefore, effective chemotherapy may reduce the risk of recurrence in resected patients and, although not curative, may palliate the symptoms, and prolong the progression-free survival (PFS) and OS of metastatic patients.

5-fluorouracil (5FU) has been the first drug showing activity in metastatic CRC. The active metabolite of 5FU is 5-fluorodeoxyuridinemonophosphate (5FdUMP), which binds and inhibits the thymidylate synthase (TS), a key enzyme in the DNA synthesis. The binding of 5FdUMP to TS is increased and stabilized by the presence of N<sup>5</sup>, N<sup>10</sup>-methylene-tetrahydrofolate, which is a metabolite of leucovorin (LV). This finding represents the rationale for the concomitant administration of 5FU and LV in CRC patients. Regimens including 5FU and LV have demonstrated to significantly increase the response rate (RR), and also to significantly prolong the PFS and OS of patients with metastatic CRC, in comparison with treatments based on 5FU alone.<sup>2</sup> Moreover, up to few years ago, LV plus 5FU, given as i.v. bolus for 5 days every 4 weeks (Mayo Clinic regimen) for 6 months, or once a week for 6–8 months (Roswell Park regimen) represented the standard postoperative treatment for surgically resected stage III and high-risk stage II colon cancer.<sup>3,4</sup> More recently, a biweekly regimen with LV 200 mg/sqm infused over 2 hours plus 5FU 400 mg/sqm i.v. bolus followed by 600 mg/sqm as 22-hour infusion for two consecutive days (LV5FU2 regimen) has replaced (at least in Europe) the above mentioned 5FU/LV regimens.<sup>5</sup>

## Single-agent Capecitabine in Metastatic CRC

Capecitabine is a pro-drug of 5FU. Taken orally, its bioavailability is almost 100%, and the plasma C<sub>max</sub> and AUC are linearly proportional to its oral dosage. After a standard single dosage of 1,250 mg/sqm, the peak plasma concentration is achieved in 1.5–2 hours. Capecitabine is then metabolized to 5FU through

3 metabolic steps. Indeed, capecitabine is converted to 5'-deoxy-5-fluorocytidine (5'-DFCR) by carboxylesterase into the liver. 5'-DFCR is then transformed to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase, an ubiquitous enzyme with high concentration in the liver, plasma, and tumor tissues. Finally, 5'-DFUR is converted to 5FU by thymidine phosphorylase (TP), which has a 3–10 times higher concentration in several solid tumors compared with the normal adjacent tissue. This higher concentration of TP leads to a 3-time higher final concentration of 5FU in tumor tissues that is than in normal tissues.<sup>6,7</sup>

Preliminary phase I–II trials conducted in metastatic CRC patients defined the recommended daily dose of the drug, which is 1,250 mg/sqm twice daily (12-hour apart) for two consecutive weeks, and one week of rest, repeating this treatment every 3 weeks.<sup>8</sup> Two phase III randomized trials compared oral capecitabine with the Mayo Clinic regimen in patients with metastatic CRC. Both these trials proved that capecitabine was at least as effective as the Mayo Clinic regimen in metastatic patients<sup>9,10</sup> (Table 1). A pooled analysis of these two studies underlined that significantly fewer patients required hospitalization for treatment-related adverse events (11.6% vs. 18.8%), and that fewer physician visits were required for treatment administration with capecitabine than with 5FU/LV.<sup>11</sup> However, it should be noted that oral capecitabine has never been compared with the LV5FU2 regimen, which has been demonstrated to be more active and less toxic than the Mayo Clinic regimen in the metastatic setting.<sup>12</sup>

Given its good toxicity profile, and the patients preference for an oral therapy,<sup>13–15</sup> capecitabine has been assessed in a phase II trial for the treatment of elderly (aged  $\geq$  70 years) patients affected by metastatic CRC. In this study, the RR was 24%, and median PFS and OS were 7.0 months and 11.0 months, respectively. Grade  $\geq$  3 adverse events occurred in only 12% of patients.<sup>16</sup> On the basis of previously reported comparative findings, oral capecitabine could be preferable than the Mayo Clinic or Roswell Park regimen in elderly patients.

## Capecitabine in Combination Regimens for Metastatic CRC

In consideration of its low toxicity profile, capecitabine has been considered for combination with either

**Table 1.** Randomized trials comparing oral capecitabine and intravenous 5FU/LV in metastatic CRC.

Author [ref]	Regimen	RR %	FFS mo.	PFS mo.	OS mo.	Main severe toxicity
Hoff et al <sup>9</sup>	5FU/LV × 5 days monthly (Mayo Clinic)	11.6	3.1	4.7	13.3	Stomatitis (16%), HFS* (1%)
	Capecitabine 1,250 mg/sqm twice daily × 2 weeks every 3 weeks	25.8	4.1	4.3	12.5	Stomatitis (3%), HFS* (18%)
Van Cutsem et al <sup>10</sup>	5FU/LV × 5 days monthly (Mayo Clinic)	15.0	4.0	4.7	12.1	Stomatitis (13.3%), HFS* (0.3%)
	Capecitabine 1,250 mg/sqm twice daily × 2 weeks every 3 weeks	18.9	4.2	5.2	13.2	Stomatitis (1.3%), HFS* (16.2%)

\*HFS, hand-foot syndrome.

irinotecan or oxaliplatin in the first line treatment of metastatic CRC.

### Capecitabine in combination with irinotecan

Following the introduction of 5FU into the clinical practice, irinotecan has been the first drug showing a relevant activity in metastatic CRC when used as a single agent, and demonstrating in combination with 5FU/LV to produce a higher RR, and a longer PFS and OS, than 5FU/LV alone.<sup>17,18</sup>

This background represented the rationale for assessing the combination of capecitabine with irinotecan in metastatic CRC patients. Two schedules of this combination were evaluated by Bajetta et al<sup>19</sup> in a phase II randomized trial: 140 patients were allocated to receive capecitabine 1,250 mg/sqm twice daily on days 2 to 15, plus irinotecan either 300 mg/sqm on day 1 (arm A) or 150 mg/sqm on days 1 and 8 (arm B), every 3 weeks. During the study, capecitabine was reduced to 1,000 mg/sqm twice daily in both arms, and irinotecan was reduced to 240 mg/sqm (arm A), and to 120 mg/sqm (arm B), in order to decrease the occurrence of diarrhea. After this amendment, severe diarrhea was registered in 26% of patients in arm A, and in 38% of patients in arm B; RR (47% vs. 44%) and median PFS (8.3 vs. 7.6 months) were comparable. Two dosages of irinotecan, either 70 mg/sqm weekly for 5 consecutive weeks (arm A), or 300 mg/sqm (reduced to 240 mg/sqm during the trial) every

3 weeks (arm B) in combination with capecitabine 1,000 mg/sqm twice daily, days 1 to 14 and days 22 to 35, every 6 weeks, were assessed by Borner et al.<sup>20</sup> RR was comparable with the two regimens (34% and 25%, respectively). However, median PFS (6.9 vs. 9.2 months) and OS (17.4 vs. 24.7 months) were both in favor of arm B, which also caused less grade  $\geq 3$  diarrhea.

Capecitabine and irinotecan combination was assessed in randomized phase III trials. In one such trial, 430 patients were randomly assigned to receive one of the following regimens: FOLFIRI (biweekly irinotecan 180 mg/sqm, LV 400 mg/sqm, 5FU 400 mg/sqm i.v. bolus plus 2,400 mg/sqm 46-h i.v. infusion); mIFL (irinotecan 125 mg/sqm, LV 20 mg/sqm and 5FU 500 mg/sqm for 2 weeks every 3); or CapIRI (irinotecan 250 mg/sqm on day 1, and capecitabine 1,000 mg/sqm twice daily for 14 days, every 3 weeks). In all arms, patients were also randomized to receive or not celecoxib orally at 400 mg bid. The addition of celecoxib did not affected activity and toxicity of each regimen. However, CapIRI 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%) (Table 3). This observation led to the closure of this arm of the trial when bevacizumab was subsequently added (5 mg/kg biweekly, or 7.5 mg/kg triweekly) to the regimens on study. Therefore, in the second part of



**Table 2.** Activity and main severe toxicity of irinotecan-based regimen (with or without celecoxib) in metastatic CRC before and after the addition of bevacizumab.<sup>21</sup>

Results	Regimen (with or without celecoxib)			Regimen (with or without celecoxib)	
	FOLFIRI	mIFL	CapIRI	FOLFIRI + BEV*	mIFL + BEV*
	N = 144	N = 141	N = 145	N = 57	N = 60
Response rate	47%	43%	39%	60%	53%
Median PFS (mo.)	7.6	5.9	5.9	11.2	8.3
Median OS (mo.)	23.1	17.6	18.9	28.0	19.2
Diarrhea	14%	19%	48%	11%	12%
Dehydration	6%	7%	19%	5%	2%
Neutropenia	43%	41%	32%	54%	29%
60-day mortality	6.6%	5.1%	3.5%	1.8%	6.8%

\*BEV, bevacizumab.

this trial, 117 patients were allocated to receive either FOLFIRI + bevacizumab or mIFL + bevacizumab. Addition of bevacizumab increased the activity of both regimens in comparison with that previously reported without bevacizumab (RR was 57% and 69%, and PFS resulted of 9.9 and 8.3 months, respectively).<sup>21</sup> Similarly, an European Organization for Research and Treatment of Cancer trial randomly compared the FOLFIRI and CapIRI regimens with or without celecoxib. This trial was prematurely closed after the enrollment

of only 85 patients because of the occurrence of 8 early deaths: 6 deaths (5 treatment-related) occurred in the CapIRI arm, and 2 deaths (both treatment-related) in the FOLFIRI arm. In addition, 61% of patients starting the CapIRI treatment required dose reduction as opposed to only 7% in the FOLFIRI arm.<sup>22</sup>

In summary, the combination of capecitabine with irinotecan is not well tolerated because both these drugs may cause diarrhea and dehydration. Indeed, these side effects were reported more frequently than

**Table 3.** Randomized trials comparing oxaliplatin plus 5FU and oxaliplatin plus capecitabine in metastatic CRC.

Trial authors [ref]	Regimen	No. pts	RR %	PFS mo.	OS mo.	Comments on comparative G $\geq$ 3 toxicity
FOCA trial Martoni et al <sup>35</sup>	XELOX	62	43	7	NR <sup>‡</sup>	Less diarrhea and stomatitis with XELOX
	pviFOX	56	48	9	NR <sup>‡</sup>	
German trial Porschen et al <sup>36</sup>	CAPOX	241	48	7.1	16.8	More HFS* with CAPOX
	FUFOX	233	54	8.0	18.8	
Spanish trial Diaz-Rubio et al <sup>37</sup>	XELOX	171	37	8.9	18.1	Less diarrhea with XELOX
	FUOX	171	46	9.5	20.8	
US TREE-1 Hochster et al <sup>38</sup>	XELOX	48	27	5.9	17.2	Less neutropenia but more dehydration with XELOX
	bFOL	50	20	6.9	17.9	
	mFOLFOX	49	41	8.7	17.6	
NO16966 trial Cassidy et al <sup>40</sup>	XELOX	317	37	8.0	19.8	Less neutropenia but more diarrhea and HFS* with XELOX
	FOLFOX4	317	39	8.5	19.6	
French trial Ducreaux et al <sup>41</sup>	XELOX	156	39	8.8	19.9	Less neutropenia, febrile neutropenia, and neuropathy with XELOX
	FOLFOX6	150	46	9.3	20.5	
COFFEE trial Comella et al <sup>42</sup>	OXXEL	158	34	6.2	16.0	Less neutropenia and febrile neutropenia, more diarrhea with OXXEL
	OXAFUFU	164	33	6.3	17.1	

<sup>‡</sup>NR, not reported; \*HFS, hand-foot syndrome.





with the combination of irinotecan and 5FU/LV. In conclusion, the CapIRI regimen should not be recommended outside clinical trials.

### Capecitabine in combination with oxaliplatin

Several investigators assessed the combination of oxaliplatin and 5FU/LV.<sup>23–25</sup> All these studies reported a greater RR, and a prolonged PFS, with the combination regimen. However, none of these trials reported a significant prolongation of OS, likely because of the second-line treatment delivered in most patients. However, these trials strongly supported the evaluation of capecitabine in combination with oxaliplatin. A phase II trial assessed the combination of oxaliplatin 130 mg/sqm on day 1, and capecitabine 1,000 mg/sqm twice daily for 2 weeks, recycling every 3 weeks (XELOX regimen), reporting a RR of 55%, a median PFS of 7.7 months, and a median OS of 19.5 months. This regimen was extremely well tolerated. The main non-hematologic side effects were diarrhea (16%), vomiting 13%, and peripheral neuropathy (16%).<sup>26</sup> No difference in tolerability between patients younger or older than 65 years was seen.<sup>27</sup>

The good tolerability and activity of the XELOX regimen in elderly subjects was confirmed in a phase II trial specifically designed for patients aged  $\geq 70$  years. In the first cycle, dosages were 85 mg/sqm for oxaliplatin on day 1, and 1,000 mg/sqm twice daily for 2 weeks for capecitabine; in the absence of grade  $\geq 2$  toxicity, an alternated intra-patient dose-escalation of capecitabine and oxaliplatin was applied in subsequent cycles. However, after the enrollment of the first 35 patients, dose-escalation of capecitabine was no more attempted in subsequent patients, while oxaliplatin was escalated up to 130 mg/sqm in 19 of 41 (46%) patients. For the whole series, RR was 40%, the median PFS was 8.5 months, and the median OS was 14.4 months. Grade  $\geq 3$  diarrhea affected only 7% of patients receiving 1,000 mg/sqm twice daily of capecitabine.<sup>28</sup>

Similar results were reported by other investigators with the XELOX regimen in a phase II trial restricted to elderly patients: RR was 36%, median PFS and OS were 5.8 months and 13.2 months. Main severe toxicity was diarrhea, registered in 11 (22%) patients.<sup>29</sup> However, it should be noted that in a phase II trial conducted in US, 5 of the first 13 (38%) patients

treated with the XELOX regimen were hospitalized for diarrhea and dehydration. This unacceptable toxicity led to decrease the capecitabine dosage to 750 mg/sqm twice daily in the following 35 patients. Although no difference in RR was seen with the reduced dosage (37.1% vs. 38.5%), grade 3–4 diarrhea was reported in only 20% of these last patients.<sup>30</sup>

Conversely, other investigators have shown that the daily dosage of capecitabine could be further increased. Scheithauer et al<sup>31</sup> conducted a phase II randomized trial, in which 89 metastatic CRC patients were allocated to receive either the standard XELOX regimen every 3 weeks, or an intensified biweekly regimen, including oxaliplatin 85 mg/sqm on day 1, and capecitabine 1,700 mg/sqm twice daily from day 1 to 7. These investigators reported a greater RR (54.5% vs. 42.2%), and a prolonged PFS (10.5 vs. 6.0 months), with the intensified regimen, without increase of side effects (grade 3 neuropathy, 12% vs. 16%; grade 3 diarrhea, 12% vs. 9% of patients, respectively). On the other hand, a slight intensification of oxaliplatin dosage was tested in a phase II trial performed in 38 metastatic CRC patients. The OXXEL regimen, including oxaliplatin 100 mg/sqm on day 1, and capecitabine 1,000 mg/sqm twice daily from day 1 (evening) to day 11 (morning), was delivered every 2 weeks. Seven complete, and 10 partial responses were reported, for an overall RR of 45%, median PFS was 7.9 months. Only 11% of patients suffered from severe diarrhea, but grade 3 neuropathy was seen in 24% of patients.<sup>32</sup>

Some trials compared different strategies (incorporating capecitabine) for the management of patients with metastatic CRC. In the Dutch CApecitabine, IRinotecan, and Oxaliplatin (CAIRO) in advanced colorectal cancer trial, 820 patients were randomized to receive either (arm A) oral capecitabine first, followed by irinotecan in second-line, and capecitabine plus oxaliplatin in third-line, or (arm B) capecitabine plus irinotecan in first-line, and capecitabine plus oxaliplatin in second-line. In arm B, RR (41% vs. 20%,  $P = 0.0001$ ), and PFS (median, 7.8 vs. 5.8 months,  $P = 0.0002$ ) were significantly improved, but the difference in OS was not significant (median, 17.4 vs. 16.3 months,  $P = 0.3281$ ). However, it should be noted that only 36% of patients in arm A did receive third-line capecitabine plus oxaliplatin, as opposed to 53% of patients treated in second-line with this combination in arm B.<sup>33</sup>



Similarly, the British COIN trial randomly compared in 1,630 metastatic CRC patients an oxaliplatin-based regimen, with either capecitabine (66% of patients) or 5FU/LV (34% of patients), given until treatment failure (continuous treatment), or the same regimens for 3 months initially, and further 3-month treatment upon progression (intermittent treatment). The intermittent treatment produced significantly less hand-foot syndrome and peripheral neuropathy, but the median OS was 14.3 vs. 15.6 months for the continuous treatment. Therefore, the non-inferiority of the intermittent treatment could not be demonstrated.<sup>34</sup>

Several randomized trials were planned to assess whether capecitabine could substitute for 5FU (with or without LV) in combination with oxaliplatin (Table 3). In one such trial, 118 patients with metastatic CRC were randomly assigned to receive either XELOX or oxaliplatin 130 mg/sqm given on the day 1 plus 5FU 250 mg/sqm/daily as protracted i.v. infusion for 3 weeks. A similar activity was reported for these two regimens (RR, 43.5% vs. 48.2%; median PFS, 9.0 vs. 7.0 months), but the XELOX regimen caused less severe diarrhea (8% vs. 13%), and stomatitis (13% vs. 29%).<sup>35</sup>

The FUFOX regimen (5FU 2,000 mg/sqm infused over 24 hours, LV 500 mg/sqm and oxaliplatin 50 mg/sqm infused over 2 hours, given weekly for 4 weeks and 2 weeks of rest) was compared with the CAPOX regimen (oxaliplatin 70 mg/sqm on days 1 and 8, and capecitabine 1,000 mg/sqm twice daily for two weeks, recycling every 3 weeks) in 476 CRC patients by the German AIO Colorectal Study Group. A similar RR (54% vs. 48%,  $P = 0.70$ ), PFS (median, 7.1 vs. 8.0 months,  $P = 0.117$ ), and OS (median, 16.8 vs. 18.8 months,  $P = 0.26$ ) were reported for these two regimens. Unexpectedly, the CAPOX regimen was not better tolerated than the FUFOX regimen.<sup>36</sup>

The XELOX regimen was compared with a regimen of 5FU 2,250 mg/sqm (48-hour infusion) weekly and oxaliplatin 85 mg/sqm biweekly in 342 metastatic CRC patients: RR was lower with the XELOX regimen (37% vs. 46%), but PFS (median, 8.9 vs. 9.5 months) and OS (median, 18.1 vs. 20.8 months) were not significantly different. The XELOX regimen produced significantly less severe diarrhea (14% vs. 24%,  $P = 0.027$ ), but caused more hand-foot syndrome (14% vs. 5%,  $P = 0.009$ ).<sup>37</sup>

In the TREE-1 study, 147 patients were randomly allocated to receive mFOLFOX (oxaliplatin 85 mg/sqm and LV 250 mg/sqm on day 1, 5FU 400 mg/sqm i.v. bolus and 2,400 mg/sqm i.v. 46-h infusion) every 2 weeks, bFOL (oxaliplatin 85 mg/sqm on day 1, and 5FU 500 mg/sqm plus LV 20 mg/sqm i.v. on days 1 and 8) every 2 weeks, or XELOX every 3 weeks. RR was 43%, 22%, and 35%, respectively, while median PFS was 8.7, 6.9, and 5.9 months, and median OS was 19.2, 17.9, and 17.2 months, respectively. XELOX caused an unacceptable occurrence of severe dehydration (27%) in comparison with mFOLFOX (8%) or bFOL (12%), although severe diarrhea was similar (31%, 33%, 26%), and grade  $\geq 3$  neutropenia was lower (15%, 53%, and 18%, respectively).<sup>38</sup> The worse tolerability of capecitabine in US patients as opposed to patients treated in other countries has been attributed to the dietary supplementation of folic acid (which may potentiate the antiproliferative activity of capecitabine) in US.<sup>39</sup> Anyway, in the second part of this study (TREE-2 trial), when bevacizumab was added to these regimens, dosage of capecitabine in the XELOX regimen was decreased to 1,750 mg/sqm/day for two weeks. In comparison with the TREE-1 study, addition of bevacizumab was reported to improve the efficacy in all arms. Indeed, RR, median PFS and OS were 53%, 9.9 months, and 26.0 months on mFOLFOX + bevacizumab arm; 41%, 8.3 months, and 20.7 months on bFOL + bevacizumab arm; 48%, 10.3 months, and 27.0 months on XELOX + bevacizumab arm. The modified XELOX + bevacizumab regimen caused severe dehydration in 8% of patients.<sup>38</sup>

The trial NO16966 was initially designed to demonstrate the non-inferiority of XELOX in comparison with FOLFOX4 regimen in terms of PFS. However, when bevacizumab was introduced into the clinical practice, the trial was amended, and patients were also randomized to receive either a placebo or bevacizumab in addition to FOLFOX4 or XELOX, in order to demonstrate the superiority in terms of PFS of bevacizumab-containing treatments in comparison with those including the placebo. Actually, the non-inferiority of the XELOX vs. FOLFOX4 regimen was demonstrated, because the PFS was 8.0 months vs. 8.5 months, with an HR of 1.05 (97.5% CI, 0.94–1.18). Additionally, XELOX reduced the occurrence of grade  $\geq 3$  neutropenia



(7% vs. 44%), but produced more severe diarrhea (20% vs. 11%) than the FOLFOX4 regimen.<sup>40</sup> Bevacizumab did not increase the RR of either XELOX or FOLFOX4, but significantly prolonged the median PFS from 8.0 to 9.4 months in comparison with placebo ( $P = 0.0023$ ).<sup>41</sup>

A French trial randomly compared the XELOX and FOLFOX6 regimens in terms of RR. The non-inferiority of the XELOX regimen was accepted, because the 95% upper limit of the difference in RR (39% vs. 46%) was below the non-inferiority margin; median PFS was 8.8 vs. 9.3 months, and median OS was 19.9 vs. 20.5 months. XELOX significantly reduced the occurrence of neutropenia, febrile neutropenia, and neuropathy.<sup>42</sup>

Finally, a Southern Italy Cooperative Oncology Group trial randomly compared the OXXEL with the OXAFUFU regimen (oxaliplatin 85 mg/sqm on day 1, and LV 250 mg/sqm plus 5FU 850 mg/sqm on day 2), both given every 2 weeks, in 322 metastatic CRC patients. A comparable RR (34% vs. 33%), PFS (median, 6.5 vs. 6.6 months), OS (median, 16.0 vs. 17.1 months), and quality of life of patients were registered in the two arms of the trial. Overall, severe adverse events were less frequent with OXXEL (32% vs. 43%), which caused less neutropenia (10% vs. 27%) and febrile neutropenia (6% vs. 13%), but more diarrhea (13% vs. 8%), than OXAFUFU.<sup>43</sup>

A pooled analysis of six trials comparing oxaliplatin-capecitabine vs. oxaliplatin-infusional 5FU, including in total 3,494 patients, showed that RR was significantly higher for 5FU-based regimens, especially considering the results obtained without the addition of bevacizumab. However, the overall HR for PFS of patients treated with capecitabine vs. infusional 5FU was 1.04 (95% CI, 0.96–1.12), suggesting similar clinical outcome for both regimens, with the upper 95% CI clearly within the range of non-inferiority. The overall risk of death was also not different between the capecitabine-based and 5FU-based regimens (HR 1.04, 95% CI, 0.95 to 1.12).<sup>44</sup>

### Capecitabine in the salvage treatment of metastatic CRC

Some investigators have assessed the combination of oxaliplatin with oral capecitabine in the salvage setting of patients with metastatic disease. A pilot phase II parallel trial evaluated the XELOX regimen

both in untreated and in pretreated patients. RR was 49% for chemo-naïve, and 15% in fluoropyrimidine-pretreated patients.<sup>45</sup> Median time to treatment failure was 5.9 and 4.2 months, respectively, while the median OS was 17.1 and 11.5 months. The XELOX regimen was well tolerated, but 26% of chemo-naïve, and 45% of pretreated patients had a capecitabine dose reduction from the second cycle.

Subsequently, a phase III trial was conducted to demonstrate the non-inferiority of the XELOX vs. the FOLFOX4 regimen in 627 patients who had received a prior treatment with irinotecan: RR was 15.3% vs. 12.4%, median PFS was 4.8 and 4.7 months, (HR = 0.97, 95% CI, 0.83–1.14), while median OS was 11.9 vs. 12.6 months (HR = 1.03, 95% CL, 0.87–1.23). Therefore, the non-inferiority of the XELOX in terms of PFS and OS was proven. Also in this trial, the XELOX regimen produced a lower occurrence of severe neutropenia (5% vs. 35%), but a greater incidence of severe diarrhea (20% vs. 5%) and hand-foot syndrome (3.5% vs. 0.6%).<sup>46</sup>

On this background, the XELOX regimen was the backbone on which to test the addition of targeted agents in previously treated patients. Indeed, 32 patients pretreated with one prior chemotherapy regimen for metastatic disease, and/or recurred within 12 months of completion of adjuvant therapy, were treated every 3 weeks with XELOX plus erlotinib 150 mg orally throughout the whole cycle. However, due to a high incidence of severe diarrhea in the first 13 treated patients, capecitabine was reduced to 750 mg/sqm bid for the following patients. A partial response was achieved in 25% of patients, a stable disease in 44%, median PFS was 5.4 months, and median OS was 14.7 months.<sup>47</sup> Moreover, given the proven capability of bevacizumab added to FOLFOX4 to increase the RR (22.7% vs. 8.6%,  $P < 0.0001$ ), PFS (median, 7.3 vs. 4.7 months,  $P < 0.0001$ ), and OS (median, 12.9 vs. 10.8,  $P = 0.0011$ ) of patients previously treated with irinotecan and fluoropyrimidine,<sup>48</sup> ongoing trials are currently evaluating the combination of bevacizumab, erlotinib, and either FOLFOX4 or XELOX in this setting.

### Capecitabine in the Adjuvant Treatment of Colon Cancer

As above mentioned, for about fifteen years the standard adjuvant treatment for operated stage III colon





cancer patients in U.S was the Mayo Clinic or Roswell Park Hospital regimen for 6–8 months.<sup>4</sup> However, in European countries these regimens were usually delivered with a slight dose-reduction in order to improve their tolerability,<sup>3</sup> and later on they have been replaced by the LV5FU2 regimen.<sup>5</sup> This adjuvant treatment is as effective in young as in elderly patients, although older subjects are less likely to receive such therapy, usually because of concern regarding tolerability.<sup>49,50</sup>

Based on previously mentioned results in metastatic patients, oral capecitabine has also been evaluated in the adjuvant setting. Indeed, in the Capecitabine Adjuvant Chemotherapy for Colon Cancer Trial (X-ACT) patients with resected stage III colon cancer randomly received capecitabine 1,250 mg/sqm twice daily, from day 1 to 14, every 21 days, or the Mayo Clinic regimen, both for 6 months. This trial aimed at demonstrating the equivalence of capecitabine in terms of disease-free survival. Actually, the HR for this outcome was 0.87, with a 95% upper limit of confidence of 1.00, which was significantly inferior ( $P < 0.001$ ) to the required upper limit of 1.20 for accepting the equivalence. In addition, at 3 years relapse-free survival was significantly superior ( $P = 0.0407$ ), and OS showed also a trend toward superiority in favor of capecitabine (HR = 0.84,  $P = 0.0706$ ).<sup>51</sup>

### XELOX regimen as adjuvant treatment of colon cancer

The XELOX regimen has been compared with the Mayo Clinic or Roswell Park Hospital regimens as adjuvant treatment in stage III colon cancer. Safety analysis of this study has recently been reported: occurrence of grade  $\geq 3$  toxicity was in favor of the XELOX regimen for neutropenia (5.3% vs. 10.9%), febrile neutropenia (0.2% vs. 3.8%), and severe stomatitis (0.6% vs. 7.9%); however, the XELOX produced more skin (3.6% vs. 0.2%) and neurosensory toxicity (8.1% vs. 0%).<sup>52</sup> With a median follow-up of 57 months, patients treated with XELOX had a 3-year disease-free survival significantly higher than patients treated with 5FU/LV (71.0% vs. 67%,  $P = 0.0045$ ).<sup>53</sup>

Moreover, on the basis of the results of the MOSAIC trial,<sup>54</sup> the AVANT trial is currently evaluating the addition of bevacizumab (biweekly or triweekly) to either FOLFOX4 or XELOX in operated stage II–III colon cancer. Mature results are eagerly awaited, because of the disappointing findings of

the NSABP-C08 trial, which showed no significant benefit in 3-year DFS (77.4% vs. 75.5%) by the addition of bevacizumab (for 1 year) to the modified FOLFOX6 regimen given for 6 months in resected stage II–III colon cancer patients.<sup>55</sup>

### Capecitabine in the Neoadjuvant Treatment of Rectal Cancer

#### Single agent capecitabine during preoperative radiotherapy (RT)

Several phase II trials have evaluated the combination of capecitabine with preoperative RT in locally advanced rectal cancer (LARC). Kim et al<sup>56</sup> delivered two cycles of capecitabine (825 mg/sqm twice daily) and LV (20 mg/sqm/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. No grade  $\geq 3$  hematologic toxicity was registered, while severe diarrhea affected 4% of patients. De Paoli et al<sup>57</sup> evaluated a regimen of capecitabine 825 mg/m<sup>2</sup> twice daily given continuously during pelvic RT (50.4 Gy in 28 fractions) in patients with LARC. They reported a downstaging in 57% of patients, and a ypCR in 24%. Treatment was well tolerated, with only 6 patients (11%) suffering from grade 3 toxicity. The same combination of capecitabine 825 mg/m<sup>2</sup> twice daily and pelvic RT was investigated by Krishnan et al<sup>58</sup> in 54 patients (51 underwent surgery): 9 patients (24%) achieved a ypCR, and 12 patients (24%) showed microscopic residual disease. Diarrhea occurred in 2% of patients. In a retrospective case-control comparison of the safety and efficacy of capecitabine and pelvic RT in 89 patients with those registered in a matched series of 89 patients previously treated with 5FU, a similar low occurrence of grade  $\geq 3$  toxicity, and comparable local and distant failure rates, were reported by Das et al.<sup>59</sup> A large retrospective analysis was performed by Kim et al,<sup>60</sup> who compared 5FU/LV and capecitabine during preoperative RT (50.4 Gy) in 278 patients. Complete (11.3% vs. 16.1%) or nearly complete (12.9% vs. 12.9%) tumor regression was observed in similar proportions with either treatment.

In summary, in these non-randomized studies, capecitabine combined with pelvic RT was reported to obtain ypCR rates comparable to those reported with 5FU. Preliminary data of a phase III trial regarding





the activity and safety of capecitabine in comparison with 5FU as neoadjuvant or adjuvant chemotherapy associated to pelvic RT for LARC were recently reported.<sup>61</sup> In the neoadjuvant setting, capecitabine obtained a non-significantly higher rate of T-downstaging (52% vs. 39%), and N0 (71% vs. 56%) than continuous infusion 5FU. Moreover, patients treated with capecitabine experienced significantly less leucopenia (25% vs. 35%), but more hand-foot syndrome (31% vs. 2%).

### Capecitabine in combination regimens during preoperative RT

Capecitabine and weekly irinotecan during three-dimensional conformal pelvic RT (50.4 Gy) were assessed by Klautke et al<sup>62</sup> in a phase I/II trial. The recommended doses were 750 mg/sqm twice daily for capecitabine, and 40 mg/sqm weekly  $\times$  6 weeks for irinotecan. A ypCR was reported in 19% of patients. Grade 3 diarrhea was the most common toxicity, reported in 37% of patients. A subsequent phase II study was conducted with capecitabine 500 mg/sqm twice daily plus irinotecan 50 mg/sqm weekly for 5 doses during pelvic RT.<sup>63</sup> With this regimen, occurrence of grade 3 diarrhea was lower (11%). A ypCR was reported in 14% of treated patients.

Some phase I/II studies were carried-out on the combination of oxaliplatin and capecitabine during preoperative pelvic RT. Rödel et al<sup>64</sup> recommended a dose of 50 mg/sqm for oxaliplatin to be delivered on days 1 and 8 of a 2-week regimen of capecitabine (825 mg/sqm/twice daily) for two cycles during pelvic RT: ypCR was reported in 19%, and a severe diarrhea occurred in 8% of cases. These results were then confirmed in a multicentre phase II trial, performed on 110 patients with T3/T4 or N+ rectal cancer: a ypCR rate was obtained in 16%, and occurrence of severe diarrhea affected 12% of patients.<sup>65</sup> Machiels et al<sup>66</sup> treated 40 patients with oxaliplatin 50 mg/sqm weekly for 5 weeks plus capecitabine 825 mg/sqm twice daily during pelvic RT. This regimen yielded a ypCR in 14% of patients, but severe diarrhea occurred in 30% of them. Glynne-Jones et al<sup>67</sup> reported that the recommended dose for continuous oral capecitabine was 650 mg/sqm twice daily in combination with oxaliplatin 130 mg/sqm delivered every 4 weeks during pelvic RT. In the following phase II study, these investigators reported that a ypCR was achieved in 16

(19%) of 83 patients. Treatment was well tolerated, with only 9% of grade  $\geq$  3 diarrhea.<sup>68</sup>

These pilot studies prompted the implementation of a phase III trial to evaluate the addition of oxaliplatin to oral capecitabine during preoperative pelvic RT for T3 or resectable T4N0-2M0 rectal cancer. A total of 586 eligible patients were randomly assigned to receive either capecitabine 800 mg/sqm twice daily during pelvic RT (45 Gy in 5 weeks), or the same dosage of capecitabine for 5 days a week plus oxaliplatin 50 mg/sqm weekly during pelvic RT (50 Gy in 5 weeks). The oxaliplatin arm was shown to significantly increase (25% vs. 11%) the occurrence of grade  $\geq$  3 toxicity of the preoperative treatment, and produced a non-significantly greater ypCR (18.8% vs. 13.8%).<sup>69</sup> These results were paralleled by the findings of the Italian STAR-01 trial, in which 747 patients with LARC were randomly treated with 5FU continuous i.v infusion (225 mg/sqm/day) during pelvic RT (50.4 Gy), or the same treatment plus oxaliplatin 60 mg/sqm weekly for 6 weeks. Occurrence of severe toxicity (mainly diarrhea) was significantly greater (24% vs. 8%) with the combination regimen, which in contrast did not produce any meaningful difference in pathologic response with the reference regimen.<sup>70</sup>

Investigators at the Royal Marsden Hospital have tested the delivery of full-dose combination chemotherapy before a preoperative chemo-radiotherapy approach, with the aim of preventing early dissemination of micrometastases, and reducing the radiation field as a consequence of tumor shrinkage. Seventy-seven poor-risk rectal cancer patients were treated with four cycles of capecitabine plus oxaliplatin before a combined treatment with capecitabine and pelvic RT, followed by twelve further weeks of adjuvant capecitabine.<sup>71</sup> A ypCR in 21%, and only microscopic tumor foci in an additional 48% of patients, were found after surgery. However, this approach determined an unpredictable rate of toxic deaths (5%). Therefore, a full-dose primary chemotherapy before a preoperative combined treatment in LARC should still be considered experimental, and restricted to clinical trials.

### Capecitabine and cetuximab during preoperative RT

Cetuximab is a monoclonal antibody directed against the epidermal growth factor receptor (EGFR). Interestingly, the overexpression of EGFR has been



reported to be associated with tumor resistance to local RT.<sup>72,73</sup> This observation represents a strong rationale for combining cetuximab with preoperative RT for rectal cancer.

A phase I–II study proved that the addition of weekly cetuximab (loading dose of 400 mg/sqm given one week before the beginning of RT, followed by 250 mg/sqm weekly for 5 weeks) to capecitabine 825 mg/sqm twice daily given during pelvic RT was feasible, with a grade 3 diarrhea occurring in 15% of patients, but the reported ypCR rate (5%) was rather disappointing.<sup>74</sup>

Other investigators reported on the feasibility of weekly cetuximab with capecitabine 500 mg/sqm twice daily and irinotecan 40 mg/sqm weekly times 5 during pelvic RT.<sup>75</sup> Moreover, cetuximab was safely added to capecitabine (825 mg/sqm/twice daily for two weeks) and oxaliplatin 50 mg/sqm (on days 1 and 8) two cycles during pelvic RT.<sup>76</sup> However, this regimen produced in 38 patients with T3–4 and/or N+ rectal cancer a surprisingly low rate of ypCR (8%) when compared to that previously reported by these investigators with the same regimen without cetuximab.

In conclusion, additional preclinical and clinical studies are needed to better identify potentially sensitive patients, and to better define the activity of this biological agent in the preoperative radiochemotherapy treatment of LARC.

## Cost-effectiveness of Capecitabine in Colorectal Cancer

Colorectal cancer is a major public health problem in western countries. In the early 1990s, the annual cost of CRC treatment in the US was \$6.5 billion, and CRC was the second most expensive cancer type, after breast cancer, in terms of patient cost of care.<sup>77</sup> Expenses associated with the management of CRC are greater in the early stages of the disease (surgery, surveillance and monitoring programs), and in the end stage (hospitalization, chemotherapy, radiotherapy, support therapy). A retrospective, case-controlled analysis was carried-out to evaluate the costs of treating patients with metastatic CRC in the US.<sup>78</sup> According to this analysis, the economic impact of metastatic CRC increased over time. Metastatic cancer was associated with higher costs (approximately \$100,000) compared to controls. These costs were mostly due to hospitalization (38%), and specialist visits (36%).

In another retrospective study, the European Organization for Research and Treatment of Cancer analyzed the type of treatment and the relative costs of newly diagnosed metastatic CRC.<sup>79</sup> This study showed significant differences in treatment among centers and between countries, and the main cost determinants were surgery, diagnostic procedures, chemotherapy, hospitalization and outpatient visits.

## Capecitabine is cost-effective

Cost-effectiveness analyses regarding capecitabine compared with current standard treatments were conducted in several countries. A number of cost-minimization studies were performed in UK to compare oral capecitabine or UFT/LV to 5FU/LV.<sup>80–83</sup> Costs of drug acquisition, chemotherapy delivery, hospitalization, and treatment of adverse events were considered within the framework of the National Health Service. These studies showed that oral therapies resulted less expensive; this was particularly evident for capecitabine, which led to lower costs compared to Mayo Clinic, LV5FU2 or modified LV5FU2 regimen.

A further study conducted in UK showed an additional advantage of capecitabine over the standard treatment.<sup>84</sup> The switch from the infusion regimen with 5FU/LV to the oral regimen with capecitabine resulted in savings in medical staff time of about 10 hours per treated patient. Similarly, a study estimated the efficacy and costs of first-line therapy of CRC with capecitabine versus the Mayo Clinic regimen. Capecitabine had an improved efficacy (RR, PFS and OS as well as more favorable safety profile), and lower treatment costs than the 5FU/LV regimen given as an intravenous bolus.<sup>85</sup>

According to a cost-minimization study conducted in Italy<sup>86</sup> from the Italian National Health Service perspective, capecitabine resulted in a lower mean treatment cost/patient over a 6-month period. Patients treated with capecitabine required substantially fewer hospital visits for drug administration than patients treated with 5FU/LV. Moreover, medical resource use analysis showed that patients treated with capecitabine spent fewer days in hospital for the management of treatment-related adverse events than did patients treated with 5FU/LV. In addition, capecitabine reduced the requirement for expensive drugs to manage adverse events.



Finally, a cost-effectiveness study conducted in the Netherlands reported lower treatment costs with capecitabine compared with the Mayo Clinic regimen of 5FU/LV.<sup>87</sup> The study showed that the higher acquisition costs of capecitabine were counterbalanced by the lower costs incurred in the management of toxicity and the lower number of patients requiring hospitalization compared with cost involved in patients receiving the Mayo Clinic regimen.

## Cost-effectiveness of capecitabine and oxaliplatin

The combination of capecitabine and oxaliplatin was considered to be cost effective relative to the FOLFOX4 regimen.<sup>88</sup> A cost-minimization study, conducted from the healthcare payer perspective in US, estimated that the XELOX regimen was associated with a sparing of \$US 4,614/patient over a 6-month treatment period than the FOLFOX4 regimen (total costs, \$US 42,442 vs. \$US 47,056). Indeed, the increased acquisition cost of capecitabine was offset by a \$US 2,570 lower administration costs and by a \$US 2,043 lower treatment-related adverse events costs.

In summary, these results demonstrated that, despite the higher drug acquisition costs, capecitabine is more cost-effective than standard treatment for the management of CRC patients.

## Conclusions

Capecitabine represents a convenient treatment for patients with CRC cancer. Its safety profile compares favorably with the Mayo Clinic regimen in both the adjuvant and metastatic setting. The combination of capecitabine with oxaliplatin, although sometimes increasing the occurrence of gastrointestinal side effects in comparison with the corresponding combinations including infusional 5FU/LV, may improve the compliance of patients with an easy-delivered therapy. The addition of bevacizumab to the XELOX regimen is safe and effective in metastatic CRC, and is currently under evaluation in the adjuvant setting. From an economic perspective, cost-effectiveness analysis demonstrated that, despite higher acquisition costs, capecitabine appears to be more cost-effective than standard i.v. treatment for the management of CRC patients with the added advantage that patients do usually prefer oral to intravenous chemotherapy.

## Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

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