Update on Capecitabine in Colorectal Cancer

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Key Words. Colorectal cancer • Capecitabine • Oxaliplatin • FOLFOX • CapOx • CapIri • XELOX

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the potential use of oral capecitabine versus i.v. 5-FU in the treatment of colorectal cancer.
2. Explain the evolving role of capecitabine in combination with novel, targeted therapeutics.
3. Describe the role of capecitabine in combination with radiation therapy.

ABSTRACT

In combination chemotherapy for metastatic colorectal cancer, i.v. 5-fluorouracil (5-FU) can be replaced by oral 5-FU (in the form of capecitabine or another orally available analogue) without negatively affecting overall toxicity and without remarkably reducing the efficacy of treatment in terms of response rate or overall survival. Preclinical evidence of synergy has led to promising early and successfully completed studies combining capecitabine plus oxaliplatin with bevacizumab, cetuximab, and epidermal growth factor receptor tyrosine kinase inhibitors. The use of preoperative capecitabine plus radiation is achieving good rates of pathological complete response in rectal cancer. While capecitabine is generally well tolerated, its potential toxicities need careful management and may require individual dose adaption. The Oncologist 2006;11:1003–1009

INTRODUCTION

In first-line metastatic colorectal cancer (CRC), capecitabine (Xeloda®, Roche Ltd., Basel, Switzerland) is at least as active as bolus 5-fluorouracil (5-FU) and infusional 5-FU [1–6]. In stage III colon cancer, the X-Act trial showed that capecitabine is an active agent with a favorable toxicity profile [2, 3], is convenient to give, is well accepted by patients because it is oral rather than i.v. (Fig. 1) [7, 8], and may reduce overall costs compared with i.v. treatments. Furthermore, in the study comparing capecitabine with the Mayo Clinic (Rochester, MN) regimen (5-FU/leucovorin [LV]), time to progression was equivalent with Xeloda® and 5-FU/LV (median 4.6 months vs. 4.7 months, respectively) [6]. The median time to treatment failure was 4.2 months with Xeloda® and 3.6 months with 5-FU/LV. Median survival was also equivalent with Xeloda® and 5-FU/LV (12.9 months vs. 12.8 months, respectively).

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Capecitabine has been developed in combination with both oxaliplatin and irinotecan. The pivotal phase II trial in first-line metastatic CRC combined capecitabine 1,000 mg twice a day on days 1–15 with oxaliplatin 130 mg/m² on day 1, every 21 days [9, 10]. Capecitabine has also been combined in this way with 250 mg/m² irinotecan given on day 1.

Grothey et al. favor a schedule that facilitates dose adjustment by dividing oxaliplatin into two 70-mg/m² doses given on days 1 and 8 [11, 12]. A similar process is followed with irinotecan, giving 80 mg of the drug on days 1 and 8. And Scheithauer et al. in France and Austria have developed a 2-week schedule in which 3,500 mg capecitabine is given on days 1–7 and 85 mg/m² oxaliplatin on day 1, every 14 days [13]. There have so far been no completed trials formally comparing these schedules, so it is not possible to say whether they differ in efficacy and toxicity.

**NONRANDOMIZED COMPARISONS INVOLVING CAPECITABINE COMBINATIONS**

Comparisons across studies suggest that the toxicity of capecitabine plus oxaliplatin (XELOX) is generally similar to that of FOLFOX (oxaliplatin/5-fluorouracil/leucovorin) [10, 14], with the exception of a higher rate of hand-foot syndrome. There is more grade 3/4 neutropenia with the latter, but this is not reflected in a greater risk of febrile neutropenia. XELOX is also comparable with FUFOX (weekly 5-FU/folinic acid/oxaliplatin) (Table 1) [15].

The efficacy of XELOX appears similar to that of other combinations. In the international phase II trial reported by Cassidy et al., the overall survival (OS) in 96 first-line patients treated was 19.5 months [10]. The response rates (RRs) of 35%–55% obtained with the combination of capecitabine with irinotecan (CAPIRI or XELIRI) in phase II studies are comparable with those reported with 5-FU/LV and irinotecan regimens (IFL or FOLFIRI) (Fig. 2) [14, 16–21]. Table 2 provides an overview of grade 3–4 adverse events [14, 16, 18, 20]. XELIRI is associated with more neutropenia than XELOX, with approximately 20% of patients experiencing grade 3/4 events [16, 18]. However, these rates are less than with IFL or FOLFIRI [14, 20], and the incidence of febrile neutropenia reported with XELIRI was only 4% [16]. However, hand-foot syndrome, which is not seen with bolus or infusional 5-FU, is apparent in 6%–8% of patients treated with XELIRI [16, 18].

**Table 1. XELOX toxicity in comparison with that of FOLFOX and FUFOX [10, 14, 15]**

<table>
<thead>
<tr>
<th>Grade 3–4 adverse events (% patients)</th>
<th>XELOX [10] (n = 96)</th>
<th>FOLFOX [14] (n = 267)</th>
<th>FUFOX [15] (n = 118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>7</td>
<td>47</td>
<td>8</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>13</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>3</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>17</td>
<td>18</td>
<td>22</td>
</tr>
</tbody>
</table>

Abbreviations: FOLFOX, oxaliplatin/5-fluorouracil/leucovorin; FUFOX, 5-fluorouracil/folinic acid/oxaliplatin; NR, not reported; XELOX, capecitabine/oxaliplatin.
Randomized Trials
Several controlled trials have compared capecitabine-containing combinations with each other or with alternative regimens involving bolus or infusional 5-FU. A summary of the randomized trials with capecitabine regimens, which will be discussed in further detail in this section, include capecitabine/oxaliplatin (CapOx) versus capecitabine/irinotecan (CapIri); TREE-1 trial; CapOx versus FUFOX; the European Organization for Research and Treatment of Cancer study of FOLFIRI versus XELIRI ± cyclooxygenase-II inhibitor (COX II); and the adjuvant Mayo Clinic/Roswell Park (RP) versus XELOX study.

Grothey et al. undertook a multicenter, randomized phase II trial of CapIri and CapOx in 161 patients using a day-1 and -8 schedule every 3 weeks [22, 23]. Both groups received capecitabine 2,000 mg on days 1–14. Four early deaths among the first 40 patients in the CapIri arm forced a dose reduction from 100 to 80 mg/m². There was no comparable problem in the first 40 patients treated with oxaliplatin, and the dose remained unchanged at 70 mg/m² for the duration of the study. Subsequently, one further patient died within 60 days of receiving the reduced and relatively low dose of irinotecan, giving a 6% overall mortality for that arm of the trial. Two deaths were due to septic diarrhea and two to pulmonary embolism, reflecting what seems to be a general tendency to increased thromboembolic events with capecitabine. Early mortality in patients treated with CapOx was 1%. Diarrhea was more common with CapIri than with CapOx (grade 3–4 events in 23% of patients vs. 14%). Sensory neuropathy was more common with CapOx (6% vs. 1%), and rates of hand-foot syndrome were comparable (grade 2 events in 9% of CapIri patients and 7% of CapOx patients; and grade 3 in 0% and 1%, respectively). The RR with CapOx was 55% and with CapIri, 41%. Median OS in the two arms was >17 months with CapOx and 18.8 months with CapIri. (Crossover was permitted at the end of the study.)

In the randomized phase II TREE-1 trial, 150 first-line patients were randomized to FOLFOX6 (including oxaliplatin 85 mg/m², 5-FU bolus 400 mg/m², and infusional 2,400 mg/m² over 46 hours, every 2 weeks), bFOL (oxaliplatin 85 mg/m² on days 1 and 15; LV 20 mg/m²; and bolus 5-FU 500 mg/m² on days 1, 8, and 15; every 4 weeks) or CapOx (oxaliplatin 130 mg/m² day 1, capecitabine 1,000 mg/m² orally twice daily for 14 days every 3 weeks) [24]. The overall incidence of grade 3–4 adverse events was similar on FOLFOX and bFOL arms; however, a greater number of grade 3 neutropenia occurred on the FOLFOX arm (27.8% vs. 10.5%). There were more patients withdrawn due to toxicities on the bFOL compared with the FOLFOX arm (11.1% vs. 7.9%, p value not significant). CapOx had a higher incidence of grade 3–4 nonhematologic toxicities (i.e., nausea [15.6%], vomiting [15.6%], dehydration [18.8%], diarrhea [21.9%], and hand-foot syndrome [15.6%]) than the FOLFOX and bFOL arms, and more patients were withdrawn due to toxicities on the CapOx arm than the other two arms (34.4%, p = .004, Fisher’s exact test). The protocol was amended to allow for an additional 210 patients to receive bevacizumab added to each regimen and to reduce the CapOx dose by 15%.

In the German AIO (Association of Medical Oncology of the German Cancer Society) trial, 476 patients were randomized to FUFOX (5-fluorouracil 2,000 mg/m² 24-hour infusion; folinic acid 500 mg/m²; oxaliplatin 50 mg/m² on days 1, 8, 15, and 22; every 5 weeks) or CapOx (capecitabine 1,000 mg/m² twice a day on days 1–14, oxaliplatin 70 mg/m² on days 1 and 8, every 3 weeks) [25]. Grade 3–4 neuropathy was more common with FUFOX than with CapOx (25% vs. 16%). This difference was also seen in the randomized phase II study. In both the phase II and phase III studies, toxicities were comparable between the 5-FU– and capecitabine-containing arms. Comparing rates of diarrhea across these studies suggests that there may be some advantage in a fractionated day-1 and -8 schedule, as used by AIO.

Table 2. Safety of XELIRI is similar to that of FOLFIRI [14, 16, 18, 20]

<table>
<thead>
<tr>
<th></th>
<th>Grade 3–4 adverse events (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>25</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>12</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>6</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: DVT, deep vein thrombosis; FOLFIRI, irinotecan/5-fluorouracil/leucovorin; IFL, irinotecan/bolus 5-fluorouracil/leucovorin; NR, not reported; XELIRI, capecitabine/irinotecan.
RRs were in the range of 40%–50% in both arms of the AIO phase III trial and across the two arms of the TREE-1 trial. A summary of the efficacy data of these three randomized trials is provided in Table 3 [23–25]. In addition, the Spanish TTD Group has shown identical results in a randomized phase II study [26]. The large phase III trial from Roche has very recently issued a press release stating that there has been no difference in progression-free survival between FOLFOX and XELOX, with results to be presented at the European Society of Medical Oncology (ESMO) 2006 meeting.

In the Adjuvant Setting

In a phase III trial in patients with resected stage III colon cancer, we compared three arms of adjuvant chemotherapy, namely: XELOX (capecitabine 1,000 mg/m² twice a day on days 1–14 + oxaliplatin 130 mg/m² on day 1, every 3 weeks for eight cycles); i.v. bolus 5-FU/LV (Mayo Clinic regimen: LV 20 mg/m² + 5-FU 425 mg/m² on days 1–5, every 4 weeks for six cycles); and RP regimen (LV 500 mg/m² + 5-FU 500 mg/m² on day 1, weeks 1–6 in four 8-week cycles) [26]. Table 4 shows the most common treatment-related grade 3–4 adverse events. XELOX compares favorably with the other arms of the study and also to the FOLFOX4 regimen from the MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) study [27, 28].

Efficacy data from this phase III adjuvant trial will be available in 2008.

### Table 3. Response rates of capecitabine in combination in randomized trials [23–26]

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Response rate</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grothey et al. [23]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CapOx</td>
<td>80</td>
<td>51%</td>
<td>7.2 months</td>
<td>&gt;17 months</td>
</tr>
<tr>
<td>CapIri</td>
<td>77</td>
<td>41%</td>
<td>7.1 months</td>
<td>18.8 months</td>
</tr>
<tr>
<td>TREE-1 study, Hochster et al. [24]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX6</td>
<td>49</td>
<td>47%</td>
<td>8.4 months</td>
<td>17.6 months</td>
</tr>
<tr>
<td>bFOL</td>
<td>50</td>
<td>32%</td>
<td>6.9 months</td>
<td>17.9 months</td>
</tr>
<tr>
<td>CapOx</td>
<td>48</td>
<td>38%</td>
<td>5.9 months</td>
<td>17.2 months</td>
</tr>
<tr>
<td>AIO study, Arkenau et al. [25]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FUFOX</td>
<td>217</td>
<td>50%</td>
<td>8.0 months</td>
<td>18.2 months</td>
</tr>
<tr>
<td>CapOx</td>
<td>167</td>
<td>47%</td>
<td>7.0 months</td>
<td>16.6 months</td>
</tr>
<tr>
<td>TTD study, Massuti et al. [26]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FUFOX</td>
<td>348</td>
<td>43%</td>
<td>9.6 months</td>
<td>Too early</td>
</tr>
<tr>
<td>XELOX</td>
<td>348</td>
<td>37%</td>
<td>8.8 months</td>
<td>Too early</td>
</tr>
</tbody>
</table>

Abbreviations: AIO, Association of Medical Oncology of the German Cancer Society; bFOL, oxaliplatin/leucovorin/bolus 5-fluorouracil; CapIri, capecitabine/irinotecan; CapOx, capecitabine/oxaliplatin; FOLFOX6, oxaliplatin 85 mg/m²/leucovorin 350mg/5-fluorouracil bolus 400 mg/m² and infusional 2,400 mg/m² over 46 hours; FUFOX, 5-fluorouracil/folinic acid/oxaliplatin; NR, not reported.

### Integrating Targeted Agents

Work is proceeding apace on evaluating 5-FU–containing regimens in combination with monoclonal antibodies or tyrosine kinase inhibitors directed against growth factors or their receptors. The combination of capecitabine with novel agents is also being actively investigated.

In inhibition of human colon cancer xenografts, there is synergy between capecitabine and bevacizumab (Avastin®, Roche Ltd.) [29, 30]. In this model, the effect of 5-FU is additive but not synergistic. The same pattern holds for combination with EGFR inhibitors (i.e., synergistic with capecitabine and additive with 5-FU) [31, 32].

### XELOX (CapOx) in Combination with Novel Agents

Such data underpin the TREE-2 trial in which first-line patients are randomized to bevacizumab plus FOLFOX, bFOL, or CapOx [24, 33]. Preliminary data suggest that the combination with bevacizumab does not increase the overall toxicity of CapOx, nor does it have any impact on the rate of thrombosis. In TREE-2, it appears that the addition of bevacizumab to FOLFOX increases the RR by a greater amount than when bevacizumab is added to the other regimens in the TREE trial (i.e., an additional increase in RR of 19% when bevacizumab is added to the bFOL arm, of 11% when bevacizumab is added to the FOLFOX arm, and of 19% when bevacizumab is added to the CapOx arm). This may be the first evidence that the synergy seen in animal models is clinically relevant. Moreover, progression-free survival and overall survival
were higher in all bevacizumab–containing arms, with no difference between FOLFOX and XELOX (9.9 vs 10.3 and 27.0 vs 26.0 months, respectively).

Fernando et al. have recently reported a phase II trial of XELOX plus bevacizumab [34]. As has been the case in other studies, the starting 1,000-mg/m² twice-a-day dose of capecitabine had to be reduced because of toxicity (in this instance, in 40% of patients). However, although confined to 30 patients, this trial is notable in reporting the longest median progression-free survival (11.9 months) yet seen in metastatic CRC. The overall RR was 57%. This was achieved despite the dose reductions required for capecitabine. At the reduced dose, no patient experienced grade 2 or greater diarrhea. Enrollment continues using an 825-mg/m² dose of capecitabine.

The early analysis of the large Roche registration trial has very recently been released in a press statement indicating that XELOX/bevacizumab is comparable to FOLFOX/bevacizumab and therefore an excellent oral substitute for the triple standard i.v. combination.

In combination with EGFR inhibitors, a 50% RR has been reported with XELOX plus gefitinib (Iressa®, AstraZeneca, London) and a 24% RR with XELOX plus erlotinib (Tarceva®, Roche Ltd.) [35, 36]. Data from two combination studies using XELOX plus cetuximab were reported at the 2006 annual meeting of the American Society of Clinical Oncology. In both trials, XELOX could be administered at full doses when combined with cetuximab without evidence of synergistic toxicity. Response rates are promising with 57% and 60%, respectively [37, 38]. A single-arm trial from our institution used the combination in refractory patients. Interestingly, data are impressive in showing responses even when patients have had three or more lines of previous therapy [39].

**XELIRI (CapIri) in Combination with Novel Agents**

There are no data so far on the combination of XELIRI with bevacizumab. However, the combination of dose-reduced XELIRI (capecitabine 800 mg/m² twice a day, irinotecan 200 mg/m² day 1: all every 22 days) with cetuximab was well tolerated and did not show high rates of severe diarrhea in preliminary results coming from a randomized phase II trial of the AIO Group [38]. By contrast, data coming from a phase I study showed that combination of XELIRI with gefitinib resulted in unacceptably high rates of toxicity, particularly diarrhea and thrombocytopenia [40].

**Capcitabine and Radiation**

The rationale for preoperative combination with radiation is greater for capecitabine than for 5-FU. In rectal cancer, use of the combination has been well tolerated and has achieved high rates of pathological complete response [41, 42]. This is also seen when combining XELOX and XELIRI with radiotherapy [41, 43]. Also, combination of capecitabine or XELOX with cetuximab or bevacizumab in chemoradiation did not result in increased toxicity, indicating the potential role of capecitabine as backbone for further combinations [44–46].

Trial NSABP (National Surgical Adjuvant Breast and Bowel Project) R-04 will randomize patients to radiotherapy plus capecitabine ± oxaliplatin or to radiotherapy plus infusional 5-FU ± oxaliplatin. Following surgery, patients will receive FOLFOX ± bevacizumab. The PET-ACC6 (Pan-European Trials in Adjuvant Colorectal Cancer) trial will compare capecitabine/radiation followed by adjuvant capecitabine 6 months after surgery, with or without oxaliplatin.

### Table 4. Grade 3–4 adverse events by percentage of patients in the phase III adjuvant trial with XELOX and in the MOSAIC trial [26, 27]

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Phase III adjuvant trial with XELOX [26]</th>
<th>MOSAIC trial [27]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-FU/LV total (n = 838)</td>
<td>Mayo Clinic (n = 591)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17.1</td>
<td>13.5</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>7.9</td>
<td>11.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Neurosensory</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10.9</td>
<td>14.0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3.8</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; MOSAIC, Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer; XELOX, capecitabine/oxaliplatin.
DISCUSSION
The fact that capecitabine is generally well tolerated makes it suitable for combination with other cytotoxics (particularly oxaliplatin), and capecitabine and XELOX appear promising as a platform on which to add novel, targeted agents. Phase III trials are ongoing in France, the U.K., and Australia.

There is some suggestion that toxicities in the U.S. may differ from those in western Europe, and expertise is required in their management. The need for dose reduction may be greater with capecitabine than with infusional 5-FU. It would be helpful for dose scheduling to be more extensively investigated preclinically.

XELOX seems more limited in suitability for combination with novel agents, especially when diarrhea is a concern. However, combination with bevazumab should be possible.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
H-J.S. has acted as a consultant for sanofi-aventis and Roche.

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