Capecitabine in colorectal cancer

Capecitabine is an oral pro-drug that is converted, via a three-step enzymatic pathway, into the cytotoxic drug 5-fluorouracil. 5-fluorouracil has an established role in the management of patients with colorectal cancer in the adjuvant and advanced disease settings. In this article we review the available clinical data for the use of capecitabine as a single agent or in combination with other cytotoxic drugs (e.g., irinotecan or oxaliplatin), or targeted anticancer treatment (e.g., anti-EGF receptor or VEGF therapy), in patients with early-stage or advanced colorectal cancer.

**KEYWORDS:** 5FU capecitabine colorectal cancer combination chemotherapy oral chemotherapy

**Background to colorectal cancer**

Colorectal cancer is one of the three most commonly diagnosed cancers in the UK and western countries. A total of 13% of all cancers and 11% of all cancer-related deaths in the UK are attributable to colorectal cancer. This constitutes approximately 36,000 new patients and 16,000 deaths per year [1].

Systemic treatment options for patients with colorectal cancer have expanded rapidly over the last 10 years, with consequent improvements in the survival of those with either early-stage or advanced disease. For many years intravenous 5-fluorouracil (5-FU), given latterly in combination with the reduced folate leucovorin (LV) [2] and often as an infusion rather than a bolus, was the only cytotoxic agent with significant activity in colorectal cancer. 5-FU results in response rates of 15–25% in the metastatic setting and improves overall survival (OS) over best supportive care by 3.7 months [3]. The introduction of irinotecan and oxaliplatin into clinical practice in the late 1990s has resulted in a significant improvement in response rates and survival in patients with metastatic disease [4–7]. OS of 15–20 months has been routinely observed in large randomized trials performed over the last 5 years. Targeted anticancer agents such as bevacizumab, a monoclonal antibody that binds to and blocks the activity of VEGF, has shown activity in colorectal cancer, and when added to combination chemotherapy further improved OS to beyond 20 months [8]. Panitumumab and cetuximab belong to a second family of monoclonal antibodies, targeting the EGF receptor (EGFR), and have shown promising activity as single agents [9] or in combination with chemotherapy [10].

Chemotherapy also has an established role in the adjuvant setting, with 5-FU/LV resulting in a 25% reduction in the risk of death for patients with stage 3 tumors [11,12], and also providing a modest benefit for those with stage 2 disease [13]. The addition of oxaliplatin to 5-FU in patients with stage 3 disease provides a further incremental improvement in disease-free survival (DFS) and OS [14,15].

The toxicity of 5-FU chemotherapy varies dependent upon the administration schedule, with hematological toxicity and diarrhea more commonly seen with bolus regimens, and hand–foot syndrome (HFS) more common with infusional schedules [16]. Infusional 5-FU-based regimens, such as the LV5FU2 regimen (LV 200 mg/m², 5-FU bolus 400 mg/m² and 5-FU 600 mg/m² 22-h infusion days 1 and 2, q14) have shown improved response rates and progression-free survival (PFS), as well as reduced rates of severe toxicity compared with bolus 5-FU regimens such as the Mayo clinic regimen (LV 20 mg/m², 5-FU bolus 400 mg/m² and 5-FU 600 mg/m² 22-h infusion days 1 and 2, q14) [17]. Chemotherapy regimens of bolus 5-FU and irinotecan proved toxic, with high rates of severe toxicity and treatment-related deaths noted due to overlapping toxicity profiles [18,19]. The lower rates of severe toxicity seen with infusional 5-FU has made it the preferred drug for combination chemotherapy schedules. Schedules of 5-FU and oxaliplatin (FOLFOX) and 5-FU and irinotecan (FOLFIRI) have been developed based upon the LV5FU2 regimen. FOLFOX and FOLFIRI have similar efficacy [20,21] and have become internationally accepted as standard first-line chemotherapy options.
Although infusional 5-FU regimens have become a standard of care they are cumbersome and require a central venous catheter to administer chemotherapy. These devices are associated with a variety of problems at the time of insertion (e.g., bleeding and pneumothorax), as well as longer term complications such as infection and thrombophlebitis. Additionally the two-weekly LV5FU2 regimen, and the original FOLFOX and FOLFIRI regimens, required the patient to attend for chemotherapy on day 1 and again on day 2 of each cycle. This was inconvenient for the patient and modified regimens omitting the day 2 bolus 5-FU dose have been developed [22,23].

In colorectal cancer, oral fluoropyrimidines dispense with the need for a central venous catheter and an infusion pump device. 5-FU has poor oral bioavailability, which has resulted in intravenous administration being preferred [24]. However, for the reasons outlined above, the development of oral fluoropyrimidines to safely and effectively replace infusional 5-FU has been an attractive prospect. Previous studies have shown that more than 80% of cancer patients would prefer oral chemotherapy, provided this is not at the expense of efficacy. However, oral therapy is not without problems. Under-and over-compliance has been documented in patients receiving oral chemotherapy, with potential implications for efficacy or toxicity, respectively [25]. The UK National Patient Safety Agency (NPSA) produced a Rapid Response Report on the risks of incorrect dosing of oral chemotherapy in January 2008 [101]. Between November 2003 and July 2007, the NPSA received reports of three deaths and 400 patient safety incidents involving oral chemotherapy. The prominence of capecitabine (42% of such safety incidents) probably reflects, at least in part, its widespread use and relatively recent introduction into clinical practice compared with other oral cytotoxics.

### Capecitabine

Capecitabine (Xeloda®, Roche, Basel, Switzerland) is the best established of several oral fluoropyrimidines that have been developed as an alternative to intravenous 5-FU. After being absorbed intact, a three-step enzymatic process converts capecitabine into 5-FU, with the final step catalyzed by the enzyme thymidine phosphorylase (TP) (Figure 1). TP is often over-expressed in human tumors [26], so capecitabine has the potential advantage of being preferentially converted into 5-FU within tumor cells [27–29].

### Metastatic colorectal cancer

#### Single-agent activity

Initial Phase I studies with capecitabine examined three treatment schedules that were then evaluated in a randomized Phase II study: continuous administration (1331 mg/m²/day), intermittent administration (2510 mg/m²/day on days 1–14, treatment break on days 15–21) and an intermittent schedule plus LV (capecitabine 1657 mg/m²/day, LV 60 mg/day) [30]. A total of 109 patients were randomized. All three schedules had similar activity levels, with response rates of 21, 24 and 23%, respectively. The main toxicities for all three schedules were nausea, diarrhea and HFS, but hematological toxicity was minimal. The patients receiving LV were administered a lower dose of capecitabine, but had the highest rates of grade 3 diarrhea and HFS. The total dose of capecitabine delivered per cycle in the intermittent arm was significantly higher than in the continuous or LV-treated arms (387 g compared with 307 and 218 g, respectively). Based on these results, the intermittent schedule was selected for further investigation due to the higher total dose of capecitabine delivered, the planned treatment breaks and acceptable levels of grade 3 and 4 toxicity.

Two key randomized Phase III trials in Europe [31] and North America [32] with identical protocols and statistical design compared the Mayo Clinic regimen with the intermittent capecitabine schedule (2500 mg/m²/day, day 1–14, q21). They clearly met their primary objective of showing capecitabine to be equivalent to 5-FU in terms of response rate, establishing it as a standard therapy in the metastatic setting. In a pre-planned integrated analysis of these trials, capecitabine use was associated with an improved response rate (26 vs 17%; p = 0.00002) and equivalent PFS or OS [33].

In these studies capecitabine was associated with significantly lower rates of severe diarrhea, stomatitis, nausea, neutropenia and neutropenic sepsis than the Mayo Clinic regimen. HFS was the only toxicity seen more frequently with capecitabine, being severe in 16–18% of patients receiving capecitabine and less than 1% of those receiving bolus 5-FU/LV. Although the Mayo clinic regimen was considered ‘standard’ for regulatory purposes when these trials were performed, it is accepted as causing high rates of hematological and gastrointestinal (GI) toxicity, and is infrequently used in UK practice. There has been no formal comparison of standard capecitabine with infusional 5-FU regimens, but recent data from the UK Medical Research
Council (MRC) FU, Oxaliplatin, CPT-11: Use and Sequencing – 2 (FOCUS2) trial provide interesting insights. FOCUS2 assessed the use of capecitabine or modified LV5FU2 (both given at 80% of standard dose) in elderly or frail patients – the primary end point being quality of life. Both fluoropyrimidines were given with or without oxaliplatin in a 2 × 2 design [4]. With 460 patients randomized, there was no significant difference between infusional 5-FU and capecitabine in terms of response rate (p = 0.98) or PFS (hazard ratio [HR] = 1.00; p = 0.96). Lower rates of grade 3/4 nausea (1 vs 5%; p = 0.032), diarrhea (5 vs 13%; p = 0.003), lethargy (8 vs 14%; p = 0.037), HFS (0 vs 5%; p = 0.001) and any grade 3/4 toxicity (27 vs 39%; p = 0.006) were observed for the modified LV5FU2 regimen in comparison with capecitabine, but there was no difference in quality of life assessed using the EORTC QLQ-C30.

Meta-analysis of trials using mainly bolus 5-FU regimens has shown that coadministration of LV improves response rate and OS compared with 5-FU alone [2]. LV also results in increased toxicity and a lower maximum tolerated dose (MTD) of 5-FU. Likewise, in the randomized capecitabine Phase II study described previously, increased rates of toxicity were seen in combination with LV, even though the dose of capecitabine itself was lower (1657
and 2510 mg/m²/day, respectively). This may have consequences for patients previously treated with 5-FU/LV who subsequently change onto a capecitabine-containing regimen. The results of the recently published Patient Preference in Adjuvant Colorectal Therapy (PACT) trial support this notion [38]. Patients were randomized to receive a 6-week period of 5-FU/LV (425 mg/m² 5-FU/45 mg LV) or capecitabine (1250 mg/m² twice a day, days 1–14), then crossed over to the alternative therapy for a further 6 weeks; at that point they chose which regimen to receive for the final 12 weeks of planned adjuvant therapy. The trial closed early due to excessive toxicity in patients receiving capecitabine following 5-FU/LV. Five of the 18 patients (28%) receiving capecitabine first experienced grade 3/4 toxicity, but this was seen in 11 of 14 (79%) of patients who received capecitabine after 5-FU/LV. The 5-FU regimen used in this study provides comparable dose intensity with relatively low rates of toxicity compared with alternative 5-FU regimens [36]. This probably increases the apparent difference in toxicity observed between 5-FU and capecitabine. Nevertheless, the toxicity experienced with capecitabine following 5-FU/LV in PACT remains unexpectedly high.

Differences in the tolerability of capecitabine and 5-FU between patients treated in North America, Europe and Asia have been the subject of much speculation and were recently confirmed [37]. In both the metastatic and adjuvant settings, North American colorectal cancer patients treated with either capecitabine or bolus 5FU experienced increased rates of grade 3/4 toxicities. The reason for this difference is unknown [37], but dietary supplementation of folate [38] may be important.

**In combination with oxaliplatin**

Several regimens have been developed combining capecitabine with oxaliplatin. The XELOX regimen (oxaliplatin 130 mg/m², day 1; capecitabine 1000 mg/m² twice a day, days 1–14) [39,40] has been established as safe and effective in Phase I and II studies. In the Phase II study, 96 patients received XELOX, with 53 responders (response rate: 55%), and encouraging time-to-progression (TTP) and OS times (7.7 and 19.5 months, respectively). Toxicity was manageable, with oxaliplatin-related neurotoxicity the most frequently observed grade 3/4 toxicity.

A randomized Phase II study of 147 patients, the Three Regimens of Eloxatin Evaluation (TREE-1) trial, combined oxaliplatin with different fluoropyrimidine partners: infusional 5-FU (modified FOLFOX-6), bolus 5-FU (bFOL; oxaliplatin 85 mg/m²/day 1 and 15, LV 20 mg/m² followed by bolus 5-FU 500 mg/m²/day 1, 8 and 15, q28), and capecitabine (CapeOx; oxaliplatin 150 mg/m²/day 1, capecitabine 1000 mg/m² twice a day, days 1–14, q21) [41]. The subsequent TREE-2 study assessed the addition of bevacizumab to this chemotherapy. In TREE-1, grade 3/4 toxicity during the first 12 weeks of treatment was seen in 67% of CapeOx and 59% of FOLFOX-6 patients, with response rates of 27 and 41%, and PFS of 5.9 and 8.7 months, respectively. However, TREE-1 was not powered to make statistical comparisons, and several well-designed, prospective, randomized Phase III studies have subsequently demonstrated noninferiority (albeit with differing statistical limits) of capecitabine and infusional 5-FU in combination with oxaliplatin.

The largest such study is XELOX-1 (NO16966A [42]), which was designed to assess whether XELOX was noninferior to the standard FOLFOX4 regimen as first-line treatment for metastatic colorectal cancer. After 634 patients had been randomized, the trial design was altered to a 2 × 2 factorial design incorporating a second randomization to bevacizumab or placebo. A further 1401 patients were randomized, giving a total of 2034 patients randomized overall. An interaction between bevacizumab and the efficacy of the XELOX and FOLFOX chemotherapy regimens was excluded, allowing data for the two XELOX regimens (± bevacizumab) and the two FOLFOX regimens (± bevacizumab) to be pooled. The primary end point of the study was noninferiority of PFS; this was defined as the upper limit of the 97.5% confidence interval (CI) of the HR for PFS being less than 1.23. The prespecified criteria for noninferiority were met, with median PFS of 8.0 and 8.5 months for XELOX and FOLFOX-4, respectively (HR: 1.04; 97.5% CI: 0.93–1.16). Additionally, no major differences were noted for the secondary end points of response rate and OS. The overall burden of toxicity was similar between the two treatments. The XELOX regimen had higher rates of grade 3/4 diarrhea (20 and 11%, respectively) and grade 3/4 HFS (6 and 1%), but FOLFOX-4 was associated with higher rates of neutropenia (44 and 7%), febrile neutropenia (4.8 and 0.9%) and grade 3/4 thromboembolic complications (6.3 and 3.8%).

Two smaller Phase III studies, with less statistical power than NO16966A, have also compared XELOX with 5-FU and oxaliplatin in the first-line setting [43,44]. Ducreux et al.
randomized 306 patients to XELOX or FUOX-6; response rates, the primary end point, were 42 and 46%, respectively [43]. This satisfied the predefined criteria for noninferiority for response rate, with PFS (9.3 vs 9.7 months) and OS (19.9 vs 18.4 months) also very similar for the two arms. In the second study, Diaz-Rubio et al. randomized 348 patients to receive XELOX or FUOX (5-FU 2250 mg/m² infusion over 48 h on days 1, 8, 15, 22, 29 and 36, plus oxaliplatin 85 mg/m³ on days 1, 15 and 29 every 6 weeks) [44]. The primary end point of TTP was 8.9 months for XELOX and 9.5 months for FUOX, and the wide 95% CI exceeded the prespecified inferiority margin so noninferiority could not be concluded.

The second-line NO16967A study [45] randomized 627 patients between XELOX and FOLFOX-4, with TTP the primary end point. With a median TTP of 4.8 months for XELOX and 4.7 months for FOLFOX4, XELOX was judged noninferior to FOLFOX; OS and grade 3/4 adverse events were also similar between the two groups.

The CAPOX regimen (oxaliplatin 70 mg/m², days 1 and 8 and capecitabine 1000 mg/m², twice a day, days 1–14, q21), is an alternative to XELOX. CAPOX was compared with FUFOS (oxaliplatin 50 mg/m², folinic acid 500 mg/m², 5-FU 2000 mg/m² as 22-h infusions on days 1, 8, 15 and 22 every 5 weeks) by the German AIO group in a randomized trial of 476 chemo-naive patients [46]. Median PFS times for CAPOX and FUFOS were 7.1 and 8.0 months, respectively (HR: 1.17, 95% CI: 0.96–1.43), but the predefined criteria for noninferiority were not satisfied. The median OS times for CAPOX and FUFOS were 16.8 and 18.8 months, respectively (p = 0.26).

These trials show that capecitabine in combination with oxaliplatin, in particular the XELOX regimen, is associated with similar efficacy and toxicity as combinations of 5-FU and oxaliplatin. A pooled analysis of a number of these trials showed noninferiority of PFS (HR: 1.05; p = 0.25) and OS providing further support for this conclusion [47]. Combination chemotherapy with XELOX, or alternative regimens, and targeted agents such as bevacizumab are likely to be increasingly used. Combining one or more targeted agents to overcome mechanisms of chemotherapy resistance and improve treatment efficacy is a promising strategy. However, as is discussed later, preliminary data from studies suggest that in some circumstances this approach may actually increase rates of toxicity and shorten survival times in patients receiving combinations of targeted agents [48,49].

**In combination with irinotecan**

Several studies of combination chemotherapy with irinotecan and capecitabine have highlighted concerns over efficacy and toxicity [50,51]. The Bolus, Infusional, or Capecitabine with Camptosar-Celecoxib Trial (BICC-C) study randomized patients to FOLFIRI (irinotecan 180 mg/m² day 1, 5-FU 400 mg/m² bolus, 5-FU 600 mg/m² 22-h infusion on days 1 and 2, LV 200 mg/m² days 1 and 2, q14), bolus irinotecan and 5-FU (mIFL, irinotecan 125 mg/m², LV 20 mg/m², 5-FU bolus 500 mg/m², days 1 and 8, q21) and capecitabine and irinotecan (irinotecan 250 mg/m² on day 1, capecitabine 1000 mg/m² twice daily, days 1–14, q21) [50]. After 430 patients had been randomized, the capecitabine-containing arm was discontinued due to increased rates of grade 3/4 toxicity (nausea and vomiting, diarrhea, dehydration and HFS) and significantly shorter PFS than FOLFIRI (5.8 vs 6.7 months; p = 0.015). The same capecitabine/irinotecan (CAPIRI) regimen was also assessed in the EORTC 40015 trial, which aimed to demonstrate noninferiority with the FOLFIRI regimen [51]. After 85 patients had been randomized, the trial was stopped due to safety concerns. Six deaths, five thought to be treatment-related, were noted in the capecitabine arm compared with two deaths in the FOLFIRI arm. The combined frequency of grade 3/4 toxicity events was higher for CAPIRI than FOLFIRI (74 vs 49%), with diarrhea the most common severe toxicity experienced with CAPIRI. A number of the patient deaths in this trial were attributed to diarrhea and/or thrombo-embolic phenomena. CAPIRI also appeared to have inferior PFS to FOLFIRI (5.8 vs 6.7 months). Both these trials included a randomization to receive celecoxib or placebo, but there is no suggestion from the data presented thus far that celecoxib contributed to the toxicity of these regimens.

Interestingly, these problems echo those seen with bolus 5-FU in combination with irinotecan, where deaths due to gastrointestinal toxicity, neutropenic sepsis and thromboembolic phenomena have been noted [18,19]. However, the large randomized Phase III Capecitabine, Irinotecan, Oxaliplatin (CAIRO) trial comparing first-line combination chemotherapy to sequential administration of the same drugs used first-line CAPIRI in one of the treatment arms, and no efficacy or safety concerns were noted [52].
The AIO study presented at ASCO in 2008 also suggests there may be a place for capecitabine in combination with irinotecan [58]. A total of 255 patients received bevacizumab 7.5 mg/kg with either capecitabine (800 mg/m²/day for 14 days) plus irinotecan (200 mg/m²) or XELOX; treatment was repeated 3-weekly. Efficacy of the irinotecan and oxaliplatin-based regimens was very similar in terms of the primary end point of 6-month PFS (84 and 78%, respectively), median PFS (12.5 and 9.9 months) and response rate (55 and 54%); grade 3/4 diarrhea was seen in both arms (15 and 19%), but neuropathy only in the oxaliplatin arm (23%). This suggests that by modifying the dose capecitabine and irinotecan can be combined effectively.

Combinations with targeted agents
The targeted agents that have been evaluated in patients with colorectal cancer are the monoclonal antibodies bevacizumab [8], targeting VEGF, and cetuximab [10] and panitumumab [9], both directed at the EGFr receptor.

The randomized Phase II TREE-2 study [41] assessed the addition of bevacizumab to the three TREE-1 regimens (mFOLFOX-6, bFOL and CapeOx, with capecitabine dose reduced from 1000 to 850 mg/m²) in 223 patients. CapeOx and mFOLFOX-6 were very similar with respect to grade 3/4 toxicity (56 and 59%), response rates (46 and 52%) and TTP (10.3 and 9.9 months).

The much larger Phase III XELOX-1 study, described above in the context of comparing XELOX to FOLFOX-4, recruited a total of 1401 patients after it had been modified to include a randomization to bevacizumab or placebo [54]. No interaction between the fluoropyrimidine used and the benefit of bevacizumab was noted by an interaction test. In the trial as a whole the addition of bevacizumab to chemotherapy (FOLFOX-4 and XELOX arms pooled) resulted in an improvement in PFS from 8.0 to 9.4 months (HR: 0.83; 97.5% CI: 0.72–0.95). In contrast to previous studies of bevacizumab, the improvement in OS did not reach statistical significance (21.3 vs 19.9 months, HR: 0.89; 97.5% CI: 0.76–1.03). A planned subset analysis of the FOLFOX-4- or XELOX-treated patients was subsequently performed. A significant improvement in PFS amongst patients receiving XELOX and bevacizumab, compared with placebo, was noted (HR: 0.77; 97.5% CI: 0.63–0.94), but no difference in PFS was noted for FOLFOX-4 ± bevacizumab (HR: 0.89; 97.5% CI: 0.73–1.08). An exploratory analysis suggested that patients randomized to FOLFOX-4 who had not received prior adjuvant therapy may benefit from bevacizumab, but not those who had received adjuvant treatment; whether this effect is real or not remains unknown. The study also looked specifically at the safety of bevacizumab, but no safety concerns for its use in combination with XELOX were noted.

Combining targeted agents given with chemotherapy is an attractive approach. The CAIRO2 trial investigated targeting both the VEGF and EGFR pathways in patients randomized to receive XELOX and bevacizumab with or without cetuximab [59]. Combining several targeted agents to overcome mechanisms of resistance to chemotherapy is an attractive proposition. A manageable increase in the overall incidence of grade 3/4 toxicity events was noted in the cetuximab arm (81 vs 72%; p = 0.03). This was largely due to increased rates of skin and nail toxicity, but the rate of other hematological and nonhematological toxicities did not vary significantly. Efficacy data were presented at ASCO 2008 [48]. Surprisingly, PFS was significantly shorter in patients randomized to receive cetuximab (9.6 and 10.7 months, respectively). RAS genotyping was performed on the majority of tumors; the negative impact of cetuximab was seen in patients whose tumors carried KRAS mutations, but not those that were wild-type (p = 0.04 and p = 0.1, respectively). The Panitumumab Advanced Colorectal Cancer Evaluation Study (PACCE) randomized patients receiving chemotherapy (FOLFOX or FOLFIRI) and bevacizumab to receive panitumumab, a fully humanized anti-EGFR monoclonal antibody. PACCE was discontinued prematurely due to excessive toxicity and reduced PFS in the panitumumab-containing arm [49].

The similar results of CAIRO2 and PACCE suggest that there may be problems combining VEGF- and EGFR-targeted agents, and support the careful evaluation of each combination prior to widespread use.

Capecitabine in the adjuvant setting
The Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial randomized patients with stage 3 colon cancer to receive the Mayo Clinic bolus 5-FU/LV regimen or capecitabine (1250 mg/m²; twice a day, days 1–14, q21) [56]. The primary end point of the trial was 3-year DFS and the study was powered to assess noninferiority of capecitabine over 5-FU. A noninferiority margin was defined by a HR with an upper limit

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of 1.25 for DFS; a separate equivalence analysis was performed using a HR with an upper limit of 1.20. In the event of equivalence being shown, a test for superiority of capecitabine over 5-FU was planned.

The 3-year efficacy analysis demonstrated a HR of 0.87 (0.75–1.00) for capecitabine compared with 5-FU, meeting the prespecified criteria for both noninferiority and equivalence; results for OS were similar, with a HR of 0.84 (HR: 0.69–1.01). These data were recently updated with median follow-up of 6.8 years, and confirmed that capecitabine was at least equivalent to 5-FU, with a trend to superiority. With further follow-up DFS was 60.8 and 56.7% for capecitabine and 5-FU, respectively; this confirmed equivalence with a HR of 0.88 (95% CI: 0.77–1.01; p = 0.0001), although this improved DFS it did not reach statistical significance (p = 0.07). Similarly, OS was 71.4 and 68.4% for capecitabine and 5-FU, respectively (HR: 0.86; 95% CI: 0.74–1.01); again the benefit for capecitabine did not reach statistical significance (p = 0.06) [57]. Interestingly, an unplanned analysis suggested greater benefit from capecitabine in patients who experienced some degree of HFS.

Mirroring data from the metastatic setting, capecitabine was better tolerated than bolus 5-FU/LV. The incidence of diarrhea, nausea and vomiting, stomatitis, alopecia, neutropenia and neutropenic sepsis were all significantly lower in the capecitabine group. Consistent with the reduced rates of severe toxicity, the use of supportive treatments such as anti-diarrheals, anti-emetics and granulocyte colony-stimulating factor was significantly lower in patients receiving capecitabine. In the context of the UK National Health Service (NHS) capecitabine brought cost savings of approximately €5348/patient, the greater drug costs of capecitabine being more than outweighed by savings in the costs of drug administration [58]. An independent Health Technology Assessment (HTA) of capecitabine in the adjuvant setting [59] similarly concluded that the use of capecitabine was indeed cost-effective in comparison with bolus 5-FU/LV.

There is increasing use of adjuvant combination therapy since the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) and National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trials showed improvement in DFS with the addition of oxaliplatin to 5-FU [14,60]. Large adjuvant trials of capecitabine in combination with oxaliplatin are in recruitment or follow-up. The XELOX-A trial compared bolus 5-FU/LV, (using either the Mayo Clinic or Roswell Park regimens) with XELOX in patients with stage 3 colon cancer [61]. Efficacy data are awaited, but analysis of toxicity showed XELOX to be safe and tolerable in the adjuvant setting. Accrual is also complete to the AVastin AdjuvaNt Trial (AVANT) study (Roche), again in patients with stage 3 disease, comparing FOLFOX-4 as standard therapy to the same regimen plus bevacizumab and to XELOX plus bevacizumab. By contrast, the ongoing UK Quick And Simple And Reliable (QUASAR2) trial in patients with stage 2 or 3 colorectal cancer compares single-agent capecitabine with and without bevacizumab.

Expert commentary

Capecitabine is an effective therapy in patients with colorectal cancer. As a single agent in patients with metastatic disease it shows similar activity to both bolus 5-FU and the LV5FU2 regimens, but with greater convenience to the patient. Capecitabine in combination with oxaliplatin, predominantly in the XELOX regimen, has been shown to be safe, effective and convenient. A number of studies have shown equivalence of XELOX compared with the standard FOLFOX regimen. The toxicity profiles of capecitabine and infusional 5-FU-based chemotherapy vary, with HFS, nausea and vomiting and diarrhea more frequently experienced with capecitabine. The extent to which capecitabine should replace intravenous 5-FU is debated, but capecitabine is already considered a standard therapeutic option in many clinical settings.

In the adjuvant setting, single-agent capecitabine is a proven alternative in patients with stage 3 colorectal cancer, and a very reasonable option in selected patients with stage 2 disease. Efficacy results of the XELOX regimen in stage 3 patients are awaited but, given the equivalence of this regimen with FOLFOX, it is likely that XELOX will become a standard adjuvant regimen.

In contrast to the encouraging data with XELOX, some safety concerns remain with respect to the combination of irinotecan and capecitabine, which has been associated with excess rates of severe toxicity and reduced efficacy; further clinical trial data are required before this combination can be considered safe and effective for routine clinical use. The finding of regional differences in the toxicity of fluoropyrimidine chemotherapy is intriguing, currently unexplained and requires further investigation.
Future perspective
The data presented above indicate that capcitabine can be considered as a safe, effective and convenient alternative to intravenous 5-FU in patients with early-stage and advanced colorectal cancer. There is accumulating evidence for the equivalence of capcitabine/oxaliplatin regimens compared with 5-FU/oxaliplatin. This is likely to lead to the increasing use of capcitabine regimens over the next few years. Many ongoing clinical trials are assessing capcitabine ± oxaliplatin in combination with targeted agents such as bevacizumab or cetuximab, and are also likely to establish capcitabine in this context. We can therefore expect that capcitabine will become a more widely used and convenient alternative to intravenous 5-FU over the coming years.

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Executive summary
- Capcitabine is an oral fluoropyrimidine designed to be converted to 5-fluorouracil (5-FU) in a three-step enzymatic reaction. The final step is catalyzed by the enzyme thymidine phosphorylase, which is frequently overexpressed in tumor cells, and results in preferential production of 5-FU in tumor cells.
- Full-dose capcitabine is tolerated less well in North America compared with Europe and Asia; this may be explained by folate status, since the use of capcitabine immediately after 5-FU and leucovorin is also associated with increased toxicity.

Capecitabine has an established role in patients with metastatic disease
- Single-agent capcitabine achieves higher response rates and similar progression-free survival and overall survival compared with bolus 5-FU.
- The combination of capcitabine and oxaliplatin is safe and effective, with several trials showing noninferiority of capcitabine to 5-FU.
- The addition of bevacizumab adds significantly to the efficacy of capcitabine and oxaliplatin.
- Combining capcitabine and irinotecan has been associated with safety concerns, but recent data suggest this regimen may have a role in combination with bevacizumab.

Capecitabine is also an effective option as adjuvant therapy
- Updated results confirm that single-agent capcitabine is at least as effective as bolus 5-FU/leucovorin, with strong trends to superior disease-free and overall survival, and better tolerability.
- Preliminary data using capcitabine and oxaliplatin with bevacizumab have identified no additional safety concerns; efficacy data are awaited with interest.

Bibliography
Papers of special note have been highlighted as:
* of interest
** of considerable interest
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33 Large randomized, controlled trial conducted comparing oxaliplatin in combination with capecitabine or 5-FU, which demonstrated noninferiority of the two regimens.

**Randomized, controlled trial assessing the CapeRI combination regimen in comparison with the FOLFIRI, and highlighted concerns regarding the toxicity of capecitabine/irinotecan combinations.**


**Website**


www.npsa.nhs.uk/nrls/alerts-and-directives/rapidr/