The integration of oral capecitabine into chemoradiation regimens for locally advanced rectal cancer: how successful have we been?

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The aim was to review available literature on capecitabine-based chemoradiation regimens for the preoperative treatment of patients with locally advanced rectal cancer (LARC) and determine efficacy and safety data for capecitabine in this setting. Medical literature databases (Pubmed, Medline) and abstracts/posters presented at recent scientific congresses (ASCO, ASTRO, ESTRO and ECCO) were screened and critically analysed to identify relevant data. A number of phase I/II studies have demonstrated that capecitabine is effective and well tolerated in combination with preoperative radiotherapy in patients with LARC. Phase III studies are ongoing. Continuous oral administration of capecitabine (825 mg/m² twice daily for 7 days/week) is an effective regimen and has similar tolerability to the less dose-intensive intermittent regimens of capecitabine given 5 days/week followed by 2 days’ rest or 14 days followed by 7 day’s rest as used in systemic chemotherapy for patients with colorectal or breast cancer. Capecitabine chemoradiation is associated with a relatively low rate of grade 3/4 adverse events. Capecitabine simplifies chemoradiation and provides a convenient treatment option for both patients and health care professionals. Combining capecitabine with cytotoxic agents such as oxaliplatin and irinotecan has the potential to further improve antitumour efficacy in patients receiving preoperative chemoradiation. Data from phase I/II single-agent and combination capecitabine chemoradiation studies provide a clear rationale for replacing infusional 5-FU with oral capecitabine as part of chemoradiation for patients with LARC.

introduction

Of the 146,940 new cases of colorectal cancer estimated to occur in the USA in 2004, almost one-third (40,570) affected the rectum alone [1]. Improved staging and surgical techniques, such as total mesorectal excision (TME), mean that local relapse rates above 10%–15% are no longer acceptable in patients with resectable rectal cancer. However, locoregional recurrence remains an important cause of morbidity and mortality following surgery, contributing to a variable 5-year survival rate (30%–70%) for patients with locally advanced rectal cancer (LARC).

Accepted methods of defining preoperatively either locally advanced rectal cancer, borderline resectable or unresectable disease would be helpful to indicate the risk of local pelvic relapse. In the UK, magnetic resonance imaging (MRI) is considered an accurate method of predicting the likelihood of the surgeon failing to achieve a negative circumferential margin/R0 resection [2, 3]. A large European multicentre study of patients with rectal cancer (Mercury Study) has prospectively validated this approach [4]. Hence clinicians can now select patients appropriate for preoperative chemoradiation.

The application of pre- or postoperative radiotherapy, either with or without systemic chemotherapy, improves local control and overall outcome in patients undergoing surgery for resectable disease. In the USA and Germany, chemoradiation has been most commonly applied postoperatively [5, 6]; in contrast, preoperative chemoradiation is favoured in many European countries [7]. A meta-analysis involving a systematic overview of 8507 patients from 22 randomised trials comparing outcomes of surgery for rectal cancer combined with preoperative or postoperative radiotherapy with those of surgery alone, show conclusively that preoperative chemoradiation reduces the risk of local recurrence in patients with resectable disease [8]. The analyses also show that the degree of benefit is greater when patients receive a biologically effective dose of radiotherapy (>30 Gy) preoperatively. The German CAO/ARO/AIO-94 study compared preoperative 5-fluorouracil (FU)-based chemoradiation with postoperative combined-modality treatment for stage II/III resectable rectal cancer. Results showed improved loco-regional control and less acute and late toxicity with preoperative treatment compared with postoperative treatment [9]. These data are likely to increase further the use of preoperative chemoradiation. A recently completed trial by the
European Organization for the Research and Treatment of Cancer (EORTC), in which patients were randomised to either preoperative chemoradiation or radiotherapy alone [10], will hopefully clarify the impact of chemotherapy when added to radiation in patients with resectable T3/T4 rectal cancer.

The fluoropyrimidine 5-FU is the most widely used radiation sensitiser in clinical practice. A large number of retrospective and prospective studies have confirmed the combination as effective in a range of gastrointestinal malignancies. Preoperative 5-FU-based chemoradiation has increasingly become part of standard therapy for patients with LARC, providing effective downstaging in the majority of patients and pathologic complete response (pCR) rates of around 10%–30% [11–16]. However, attempts to improve the efficacy of bolus 5-FU-based postoperative chemoradiation by incorporation of semustine or modulation through the addition of leucovorin (LV) and/or levalloisole have failed to demonstrate any significant benefits over 5-FU alone [17–19]. The Intergroup 0144 study randomised 1917 patients to receive postoperative radiation in combination with either bolus or protracted venous infusion (PVI) 5-FU and demonstrated that disease-free survival (DFS) and overall survival were similar for both regimens [20]. However, toxicity appeared to be lower in the PVI 5-FU arm. In another study, administering 5-FU as a protracted infusion in conjunction with postoperative radiotherapy improved DFS and overall survival compared with bolus administration of 5-FU [21]. Yet, central venous or peripheral lines are both cumbersome and inconvenient for patients, and associated with sepsis and thrombotic problems, which may require additional hospital visits.

Consequently, current aims in rectal cancer management are to ensure the appropriate selection of patients for preoperative chemoradiation and to improve outcome, while minimising treatment-related toxicity. Furthermore, many existing regimens were not developed through formal phase I/II studies and most have not been compared directly. In light of the proven efficacy and safety benefits of the oral fluoropyrimidine capecitabine (Xeloda®) over bolus intravenous 5-FU/LV in the treatment of metastatic colorectal cancer [22, 23] and early-stage colon cancer [24, 25], a number of studies are evaluating capecitabine as a replacement for 5-FU/LV in chemoradiation schedules for patients with rectal cancer. Beyond the increase in convenience of using oral agents, there is also a clear preclinical rationale for improved efficacy through the combination of systemically active agents, and a reduction in the toxicity associated with radiotherapy. This report reviews the rationale and clinical experience with capecitabine-based chemoradiation in patients with LARC.

**Rationale for capecitabine-based chemoradiation**

Capecitabine is an oral, tumour-activated fluoropyrimidine carbamate that delivers 5-FU preferentially to tumour cells via a three-step *in vivo* enzymatic conversion. The final step is mediated by the enzyme thymidine phosphorylase (TP), which is upregulated in tumour tissue compared with adjacent healthy tissue [26, 27]. There is a potential therapeutic advantage to the use of capecitabine in combination with radiation. Exposure of normal tissues to 5-FU within the radiation field is likely to be lower with oral capecitabine compared with intravenous 5-FU. This was demonstrated in a study conducted in 19 colorectal cancer patients that compared 5-FU concentrations in primary tumour and adjacent normal tissue, liver metastasis and adjacent normal tissue, and plasma following administration of capecitabine [26]. Through its twice-daily oral administration, capecitabine approximates continuous infusions of 5-FU.

Capecitabine also has proven activity as both adjuvant and first-line treatment for colorectal cancer. The results from two large, randomised phase III trials including over 1200 patients showed that oral capecitabine was more active than bolus 5-FU/LV in terms of tumour response (26% versus 17%), and produced at least equivalent time to disease progression (TTP) and overall survival [22], with an improved safety profile. Efficacy and safety are mirrored in the adjuvant setting, with recently published data from a large phase III trial of 1987 patients with Dukes’ C colon carcinoma showing a significant improvement in relapse-free survival and trends towards superior disease-free and overall survival [24]. Pharmacoeconomic benefits in terms of medical resource utilisation and other cost savings have also been reported with capecitabine in the metastatic and adjuvant settings [28–30].

Capecitabine has at least additive activity when administered 1 h before radiotherapy in WiDr human colon cancer xenografts, while 5-FU given alongside radiotherapy has no clear additive effect (Figure 1) [31]. Radiotherapy enhances TP expression in human tumour xenograft models, with single-dose irradiation resulting in a 13-fold increase in intratumoral TP activity (Figure 2) compared with no upregulation in healthy liver tissue [31]. This upregulation of TP by radiation may increase the preferential delivery of 5-FU to the site of the tumour following the administration of capecitabine. Compared with continuous infusions of 5-FU, oral capecitabine in combination with radiotherapy is convenient for patients and health care professionals. Capecitabine also avoids the potential
complications associated with indwelling central venous catheters, such as infections, sepsis, thrombosis and blockage [32–34]. Finally, the preferential delivery of 5-FU to the site of the tumour means that capecitabine-based chemoradiation may have an enhanced therapeutic ratio compared with 5-FU-based treatment in patients with LARC.

In terms of timing of capecitabine and radiotherapy, in the xenograft experiments capecitabine was administered 1 h before radiotherapy. However, the $t_{\text{max}}$ for capecitabine and its metabolites (including 5-FU) are identical at 2 h post-ingestion [35]. For this reason, we would recommend administering capecitabine a minimum of 2 h before morning radiotherapy in the clinic.

development of hyperglycaemia in a patient with diabetes. All patients had hyperglycaemia in a patient with diabetes. All patients except a period during the study period [49]. TME was performed 6 weeks after the completion of chemoradiation in 38 patients. The overall downstaging rate was 90%. Fifty-two patients underwent radical surgery with pCRs in 17% and microscopic residual disease in a further 15% (Table 1). Tumour and nodal downstaging was observed in 62% of patients. Again a low rate of grade 3/4 adverse events was observed.

phase II/III studies

Dunst et al. are currently performing an expanded phase II trial of their earlier phase I dose-finding study [38]. The majority of adverse events in the 58 patients evaluable for safety were mild to moderate in intensity. The only grade 3 treatment-related adverse events were leuko- and lymphocytopenia (10%), diarrhoea (4%), hypokalaemia (4%) and local skin erythema in the radiation fields, bilirubin increase, hypocalcaemia, and hyponatraemia in one patient each. No treatment-related grade 4 clinical or laboratory events were reported, except a period of hyperglycaemia in a patient with diabetes. All patients underwent radical surgery, the majority with free margins (R0 resections, 89%, Table 1). A high rate of tumour downstaging was observed on histology (73%).

A phase II study conducted at the MD Anderson Cancer Center in the USA [39] included 54 patients who received preoperative radiotherapy (45 Gy given in 25 fractions to the pelvis with a boost to deliver 52.5 Gy given in 30 fractions to the primary and perirectal nodes) plus continuous oral capecitabine (825 mg/m$^2$ twice daily) for 5 weeks. Overall response rate after chemoradiation was 90%. Fifty-two patients underwent surgery with pCRs in 17% and microscopic residual disease in a further 15% (Table 1). Tumour and nodal downstaging was observed in 62% of patients. Again a low rate of grade 3/4 adverse events was observed.

Other prospective phase I/II studies of capecitabine chemoradiation have been conducted in China [40], the Czech Republic [41], France [42], Greece [43], Italy [44, 45], Thailand [46], the UK [47] and the USA [48], with results being similar to those from the earlier German and US trials (Table 1).

A Korean phase II study added leucovorin (20 mg/m$^2$/day) and administered two cycles of intermittent oral capecitabine (825 mg/m$^2$ twice daily) for 14 days followed by a 7-day rest period [49]. TME was performed 6 weeks after the completion of chemoradiation in 38 patients. The overall downstaging rate was 84%, and 31% of patients achieved a pCR (Table 1). No grade 3/4 haematological adverse events occurred; other grade 3 events included HFS (7%), fatigue (4%), diarrhoea (4%) and radiation dermatitis (2%). The addition of leucovorin (LV) does not appear to enhance the efficacy of capecitabine and is therefore not generally recommended.

experience with single agent capecitabine chemoradiation in LARC

dose-finding studies

Two phase I dose-finding studies were conducted to determine the maximum tolerated dose (MTD) of capecitabine in combination with standard radiotherapy as pre- and/or postoperative therapy in patients with LARC [36, 37]. In the first study, patients received continuous capecitabine (250–1250 mg/m$^2$ twice daily, 7 days/week) plus radiotherapy (50.4 Gy in 1.8 Gy daily fractions) for approximately 6 weeks in the neoadjuvant, adjuvant or palliative settings [36]. Treatment demonstrated promising activity in 36 patients with rectal cancer, leading to one pathological complete response (pCR) and nine partial responses (PR) in the 10 patients treated in the preoperative setting. No grade 3/4 adverse events occurred in patients who received the authors’ recommended dosing regimen of continuous capecitabine 825 mg/m$^2$ twice daily in combination with standard radiotherapy. Dose-limiting toxicity (DLT) at higher doses was hand–foot syndrome, but no increase in radiation-related toxicities was observed.

In a second study, the MTD of capecitabine was reached at a dose level of 1000 mg/m$^2$ twice daily administered for 5 days (Monday–Friday) throughout the course of preoperative pelvic irradiation (50.4 Gy) in 28 patients with potentially resectable LARC [37]. Of these, 27 underwent subsequent surgical resection, 15 had the clinical T stage reduced by at least one stage in pathologic specimens, and five patients (19%) achieved a pCR. Capecitabine 900 mg/m$^2$ twice daily in combination with radiotherapy was associated with no DLTs in eight patients and produced a low rate of hand–foot syndrome, myelosuppression, gastrointestinal adverse events and no perioperative mortality, together with acceptable post-operative complications rates.

Based on these phase I studies, several phase II trials have either been conducted or are underway to investigate the efficacy and tolerability of continuous and intermittent capecitabine chemoradiation regimens prior to surgery in patients with LARC. The majority of research has focused on the 7 days/week schedule, which is theoretically preferable as it offers more continuous exposure to capecitabine.

Figure 2. Effect of local X-ray irradiation on TP upregulation in a WiDr human colon cancer xenograft (mean TP values ± standard deviation) [31].
<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of evaluable patients</th>
<th>Treatment</th>
<th>Downstaging rate (%)</th>
<th>Response (%)</th>
<th>R0 resections (%)</th>
<th>Main grade 3/4 adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunst et al. [38]</td>
<td>69 (efficacy)</td>
<td>Pelvic RT (1.8 Gy/day) + presacral boost (3 × 1.8 Gy) + C (825 mg/m² b.i.d.) × 6 weeks</td>
<td>73</td>
<td>Clinical ORR (61) pCR (4)</td>
<td>89</td>
<td>Grade 3 leuko-/lymphocytopenia (10%), diarrhoea (4%), hypokalaemia (4%). No grade 4 clinical/laboratory events</td>
</tr>
<tr>
<td>Lin et al. [39]</td>
<td>53 (efficacy)</td>
<td>Pelvic RT (1.8 Gy/day, total 45 Gy) + primary tumour/perirectal node RT (1.75 Gy/day, total 52.5 Gy) + C (825 mg/m² b.i.d.) × 5 weeks</td>
<td>62</td>
<td>ORR (90) pCR (17)</td>
<td>NR</td>
<td>Grade 3 diarrhoea (13%), radiation dermatitis (6%) mostly in patients &gt; 65 years of age. No grade 4 events (except in one patient with idea possibly related to treatment)</td>
</tr>
<tr>
<td>Shen et al. [40]</td>
<td>71</td>
<td>Pelvic RT (1.8 Gy/day, total 60 Gy) + C (825 mg/m² b.i.d.) × 6 weeks</td>
<td>NR</td>
<td>Clinical ORR (65) pCR (15)</td>
<td>NR</td>
<td>Grade 3 HFS (3%), diarrhoea (3%), nausea (1%). No grade 4 events</td>
</tr>
<tr>
<td>Kocakova et al. [41]</td>
<td>43</td>
<td>Pelvic RT (1.8 Gy/day, total 45 Gy) + 3-fraction boost up to 50.4 Gy + C (825 mg/m² b.i.d.) × 5 weeks</td>
<td>NR</td>
<td>pCR (21)</td>
<td>NR</td>
<td>Grade 3 diarrhoea (9%), skin toxicity (4%), abdominal pain with fever (4%), Chronic post-radiation colitis (17%)</td>
</tr>
<tr>
<td>Dupuis et al. [42]</td>
<td>51</td>
<td>Pelvic RT (1.8 Gy/day, total 45 Gy) + C (825 mg/m² b.i.d.) × 5 weeks</td>
<td>NR</td>
<td>pCR (24)</td>
<td>100</td>
<td>Grade 3 diarrhoea (6%), HFS (4%). No grade 4 clinical/laboratory events</td>
</tr>
<tr>
<td>Androulakis et al. [43]</td>
<td>23</td>
<td>Pelvic RT (1.8 Gy/day, total 50.4 Gy) + C (500–900 mg/m² b.i.d.) × 5 weeks THEN 4 cycles of 5-FU/LV (Mayo regimen)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Grade 3 diarrhoea (9%), skin toxicity (4%), abdominal pain with fever (4%). Chronic post-radiation colitis (17%)</td>
</tr>
<tr>
<td>Dj Bartolemeo et al. [44]</td>
<td>11 (38 enrolled)</td>
<td>5-FU (425 mg/m²) + LV (20 mg/m²) days 1–5, q3 weeks × 2 THEN Pelvic RT (1.8 Gy/day, total 45 Gy) + C (800 mg/m² b.i.d.) × 5 weeks THEN 2 cycles of 5-FU/LV (as above)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Grade 3 proctitis (18%), diarrhoea (18%); grade 4 cystitis (9%). Therapy stopped in 18% of patients due to adverse events</td>
</tr>
<tr>
<td>De Paoli et al. [45]</td>
<td>53</td>
<td>Pelvic RT (1.8 Gy/day, total 45 Gy) + 3-fraction boost (5.4 Gy) to tumour + C (825 mg/m² b.i.d.)</td>
<td>57</td>
<td>Clinical ORR (58) pCR (24)</td>
<td>NR</td>
<td>Grade 3 events—not specified (11%). No grade 4 clinical/laboratory events</td>
</tr>
<tr>
<td>Veerasarn et al. [46]</td>
<td>27</td>
<td>Pelvic RT (1.8 Gy/day, total 45 Gy) + C (700–1200 mg/m² b.i.d.) × 5 weeks</td>
<td>42</td>
<td>pCR (14)</td>
<td>89</td>
<td>Grade 3 diarrhoea (7%). No grade 3/4 haematological events</td>
</tr>
<tr>
<td>Chau et al. [47]</td>
<td>68</td>
<td>Pelvic RT (45 Gy/25 fractions) + primary tumour boost (9 Gy) × 6 weeks + C (825 mg/m² b.i.d.)</td>
<td>79</td>
<td>Clinical ORR (97) pCR (24)</td>
<td>98</td>
<td>Grade 3: skin reaction (34%), lower GI events (6%), neutropenia (6%), genitourinary symptoms (2%), thrombocytopenia (1%). No grade 4 adverse events reported</td>
</tr>
<tr>
<td>Wong et al. [48]</td>
<td>18</td>
<td>Pelvic RT (1.8 Gy/day, total 50.4 Gy) + C (825 mg/m² bid days 1–5) × 6 weeks THEN C (1250 mg/m² days 1–14, q3 weeks) × 6 cycles</td>
<td>50</td>
<td>pCR (17)</td>
<td>NR</td>
<td>Grade 3 diarrhoea (11%), HFS (11%), cardiac toxicity (11%). No grade 3/4 haematological events</td>
</tr>
<tr>
<td>Kim et al. [49]</td>
<td>38</td>
<td>Pelvic RT (45 Gy/25 fractions) 5 days/week × 5 weeks + boost to primary tumour (5.4 Gy/3 fractions) + C (825 mg/m² b.i.d.) + LV (20 mg/m²/day) days 1–14 × 3 week, × 2</td>
<td>84</td>
<td>pCR (31)</td>
<td>NR</td>
<td>Grade 3 HFS (7%), fatigue (4%), diarrhoea (4%), and radiation dermatitis (2%). No grade 3/4 haematological adverse events</td>
</tr>
</tbody>
</table>

b.i.d., twice daily; C, capecitabine; DLT, dose-limiting toxicity; I, irinotecan; LV, leucovorin; MTD, maximum tolerated dose; NR, not reached/reported; O, oxaliplatin; ORR, overall response rate; pCR, pathologic complete response; RT, radiotherapy; TME, total mesorectal excision.
associated with more pronounced toxicity [50], so there is little interest in developing this capecitabine/LV chemoradiation regimen.

Planned/ongoing randomised phase III studies include a large National Surgical Adjuvant Breast and Bowel Project trial (NSABP R-04), which is comparing radiotherapy plus either continuous infusional 5-FU or capecitabine as preoperative therapy in patients with resectable rectal cancer. The NSABP is also looking into the addition of oxaliplatin or bevacizumab in both treatment arms. The primary aim of the study is to compare the rate of local-regional relapse in the two groups. Co-primary end points are pCR and DFS. A smaller phase III trial is underway in Germany to compare adjuvant capecitabine chemoradiation versus 5-FU chemoradiation in patients with rectal cancer. PETACC plans to conduct a neoadjuvant/adjuvant rectal cancer study comparing capecitabine single-agent versus capecitabine-oxaliplatin combination.

Consideration of the various schedules used to date suggests that reducing the dose density of capecitabine by switching from a continuous regimen to either a 5-day or 14-day regimen followed by a 7-day rest period has no safety benefits over continuous treatment. Furthermore, the continuous regimen is likely to have a more constant cytotoxic action, thereby limiting tumour regrowth. Consequently, the Dunst regimen (capecitabine 825 mg/m² twice daily given continuously in conjunction with standard radiotherapy) can be recommended as preoperative therapy for LARC.

capcitabine/oxaliplatin combinations

rationale for combining capecitabine/oxaliplatin in chemoradiation regimens

The third-generation platinum analogue oxaliplatin is a good candidate for inclusion into neoadjuvant chemoradiation regimens. Preclinical and clinical studies have demonstrated oxaliplatin to be a potent radiosensitising agent [51]. In preclinical models of combined radiotherapy and oxaliplatin, an 8-h oxaliplatin exposure has been associated with a dose-related cell kill rate [52]. Synergistic effects with radiation in colon cancer cells were observed when oxaliplatin was administered both before and after radiation. In mouse xenograft models of colorectal cancer, tumour growth has been shown to be inhibited by combined oxaliplatin and radiation [53].

Preclinical studies have also shown that combination of capecitabine and oxaliplatin is capable of inhibiting the in vivo growth of a CXF280 human CRC xenograft more effectively than either capecitabine or oxaliplatin alone, which is probably due to the upregulation of TP expression by oxaliplatin observed in the same xenograft model [54]. Supra-additive activity of the combination was also seen in a gastric cancer model.

As a preoperative regimen for initially unresectable liver metastases, oxaliplatin plus 5-FU/LV results in tumour downsizing and a good complete resection rate [55]. Results from the MOSAIC adjuvant study have shown that the addition of oxaliplatin to infusional 5-FU/LV (FOLFOX-4) improves the DFS of patients with Dukes’ B2 and C colon cancer [56]. Thirdly, when administered as first-line treatment in metastatic colorectal cancer, FOLFOX-4 and FUFOX regimens improve response rates and TTP compared with 5-FU/LV alone [57-59]. In a large phase II trial of 96 previously untreated patients, treatment with the combination of oxaliplatin (130 mg/m² i.v. on day 1) and capecitabine (1000 mg/m² twice daily on days 1–14) every 3 weeks led to objective tumour responses in 55% of patients, including 2 CRs and 51 PRs [60] with a safety profile similar to FOLFOX-4. Capecitabine/oxaliplatin combinations have also demonstrated comparable efficacy and tolerability at least as good as 5-FU/oxaliplatin combinations in two recently presented phase III trials in first-line metastatic colorectal cancer [61, 62].

clinical studies of chemoradiation with capecitabine in combination with oxaliplatin

A phase I/II study from the UK has determined the MTD of continuous (7 days) oral capecitabine administered twice daily in combination with oxaliplatin 130 mg/m² on days 1 and 29, and pelvic radiotherapy in patients with borderline or unresectable rectal cancer [63]. Eighteen patients were treated with capecitabine at three dose levels in the phase I portion of the study. DLTs occurred in two of six patients receiving capecitabine 825 mg/m² twice daily (grade 3 diarrhoea and moist desquamation), and hence 650 mg/m² twice daily plus oxaliplatin 130 mg/m² on days 1 and 29 and 45 Gy radiation was recommended as the dose for further study. A phase II study has treated a total of 78 patients with this schedule. Of the 96 patients enrolled across the two portions of this study, 95 received treatment. Following chemoradiation, 85 patients underwent a potentially curative resection, although histology is not available for two patients. Of the patients undergoing surgery, 75 (88%) had R0 and eight (9%) had R1 resections; 16 of the 83 resected specimens (19%) showed a pCR (Table 2). All of the 95 patients who received chemoradiation were assessed for safety. The analysis confirms that the recommended chemoradiation regimen is feasible. Only 21 of 95 patients (22%) experienced grade 3/4 adverse events, most common being gastrointestinal disturbances (diarrhoea, nausea, vomiting, GI pain), lethargy and dehydration. No patients withdrew prematurely due to adverse events and there were no treatment-related deaths. Now that this study is complete, the regimen is likely to be evaluated in a larger randomised phase III trial.

A German Group performed a phase I study to determine the MTD of oxaliplatin when administered with capecitabine and standard radiotherapy, and extended to a phase II neoadjuvant study in 32 patients with LARC or low-lying rectal cancer [64]. Patients received an intermittent schedule of capecitabine (825 mg/m² twice daily on days 1–14 and days 22–35) plus oxaliplatin (50 mg/m² on days 1, 8, 22 and 29) in combination with pelvic radiotherapy (50.4 Gy in 1.8 Gy daily fractions) for 5 weeks. Tumour downsizing was observed in 17/31 (55%) of operated patients, and a pCR was identified in 19% of the resected specimens (Table 2). R0 resection was achieved in 79% of patients with clinically staged T4 tumours. Adverse events observed at the recommended oxaliplatin dose level (50 mg/m²/day) were generally mild, with only two cases of short-lived grade 3 diarrhoea. Myelosuppression, mainly leukopenia, was no higher than grade 2 in 19% of patients. The authors
recommended, and are planning, that a large phase III study should be conducted in patients with LARC to compare standard 5-FU-based chemoradiation with capecitabine and oxaliplatin chemoradiation.

A Belgian trial has used capecitabine 5 days per week given on weekdays only (i.e. capecitabine 825 mg/m\(^2\) b.i.d. on days 1–14 and 22–29) + O (50 mg/m\(^2\) days 1, 8, 22 & 29) ×5 weeks followed by radical surgery 6 weeks later [65]. A high rate of grade 3/4 diarrhoea (30%) has been reported, but toxicity has been generally manageable with dose interruptions/reductions and the dose intensity of both capecitabine and oxaliplatin remained high. While the final efficacy findings have yet to be published, the current rate of downstaging is high (58%) and pCRs were identified in 14% of the resected specimens. This same regimen has also been evaluated in the larger international phase II CORE (capecitabine, oxaliplatin, radiotherapy and excision) study. The study is now closed after recruiting 80 patients and full efficacy and safety results are expected in 2006 (Sebag-Montefiore, personal communication).

Another small dose-finding study is evaluating a similar chemoradiation regimen (capecitabine 725–900 mg/m\(^2\) twice daily on weekdays plus escalating doses of oxaliplatin 50 mg/m\(^2\), 60 mg/m\(^2\), 70 mg/m\(^2\) on days 1, 8, 15, 22 and 29 plus radiotherapy 45 Gy in 1.8 Gy daily fractions for 5 weeks) [66]. However, two of six patients at the first dose level experienced DLT in terms of grade 3 diarrhoea. The authors believe that these doses were poorly tolerated and are currently evaluating a lower dose of capecitabine (725 mg/m\(^2\) twice daily) with 50 mg/m\(^2\) oxaliplatin in a larger phase II trial. Finally, an ongoing Italian study is examining preoperative capecitabine and oxaliplatin with high-dose pelvic conformal radiotherapy in LARC [67].

The current findings from the above studies suggest that preoperative capecitabine and oxaliplatin chemoradiation is effective and generally well tolerated, although more robust toxicity data on weekly schedules of oxaliplatin is required. For this reason, a large, phase III pan-European trial (PETACC-6) comparing capecitabine and oxaliplatin chemoradiation with capecitabine chemoradiation alone as adjuvant treatment in T3/4 N1/2 patients is in development.

### capecitabine/irinotecan combinations

#### rationale for combining capecitabine/irinotecan in chemoradiation regimens

The addition of the topoisomerase-I inhibitor irinotecan to infusional 5-FU (Douillard regimen) or bolus 5-FU (Saltz IFL regimen) significantly improves response rates, median time to progression (TTTP) and overall survival compared with 5-FU/LV alone in patients with metastatic colorectal cancer [68, 69].

### Table 2. Phase II/III studies of capecitabine–oxaliplatin chemoradiation regimens in patients with LARC

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of evaluable patients</th>
<th>Treatment</th>
<th>Downstaging rate (%)</th>
<th>Response (%)</th>
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<th>Grade 3/4 adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glynne-Jones et al. [63]</td>
<td>95 (safety) 85 (efficacy)</td>
<td>Pelvic RT (45 Gy/25 fractions) + C (650 mg/m(^2) b.i.d.) + O (130 mg/m(^2) days 1 &amp; 29) ×5 weeks</td>
<td>NR</td>
<td>pCR (19)</td>
<td>88</td>
<td>Grade 3/4 diarrhoea (9%), lethargy (2%), dehydration (2%), GI pain (2%)</td>
</tr>
<tr>
<td>Ro¨del et al. [64]</td>
<td>32</td>
<td>Pelvic RT (30.4 Gy/1.8 Gy/d) + C (825 mg/m(^2) b.i.d. days 1–14 and 22–35) + O (50 mg/m(^2) days 1, 8, 22 &amp; 29) ×5 weeks</td>
<td>55</td>
<td>pCR (19)</td>
<td>79</td>
<td>Grade 3: diarrhoea (6%), skin reaction (6%)</td>
</tr>
<tr>
<td>Machiels et al. [65]</td>
<td>36 (efficacy) 40 (safety)</td>
<td>Pelvic RT (45 Gy of 1.8 Gy/d) + C (825 mg/m(^2) b.i.d. weekdays) + O (50 mg/m(^2) days 1, 8, 15, 22 &amp; 29) ×5 weeks</td>
<td>58</td>
<td>pCR (14)</td>
<td>83</td>
<td>Grade 3/4 diarrhoea (30%)</td>
</tr>
<tr>
<td>Fakih et al. [66]</td>
<td>12</td>
<td>Pelvic RT (45 Gy of 1.8 Gy/d + 5.4 Gy boost) + C (725–900 mg/m(^2) b.i.d. weekdays) + O (50 mg/m(^2) days 1, 8, 15, 22 &amp; 29) ×5 weeks</td>
<td>50</td>
<td>pCR (20)</td>
<td>NR</td>
<td>Grade 3 at dose level 1 (C 825/O 50): hyponatraemia + diarrhoea in 2 patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>xlim for dose level –1 (C 725/O 50): small bowel obstruction, nausea/vomiting, dehydration and diarrhoea in 1 patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

b.i.d., twice daily; C, capecitabine; DLT, dose-limiting toxicity; I, irinotecan; LV, leucovorin; MTD, maximum tolerated dose; NR, not reached/reported; O, oxaliplatin; ORR, overall response rate; pCR, pathologic complete response; RT, radiotherapy; TME, total mesorectal excision.
addition, combining 5-FU and irinotecan in human colorectal cancer cell lines showed additive antitumour activity compared with either agent administered alone [70, 71]. However, three separate phase III trials have recently shown no efficacy advantage with the addition of irinotecan to 5-FU-based therapy in stage III colon cancer [72–74]. This makes the rationale for using irinotecan in the neoadjuvant setting far less convincing than for oxaliplatin. However, the sequential combination of low doses of irinotecan (day 1) followed by capcitabine (days 2–15) is curative and selective against human A253 and FaDu head and neck xenografts in nude mice [75]. Finally, in nude mice bearing HCT-8 or HT-29 human colon cancer xenografts, the combination of irinotecan and capcitabine was significantly more active than either agent alone when administered at their MTDs [76]. Preclinical studies have demonstrated irinotecan to be a potent radiosensitising agent in human lung tumour xenografts [76] and colorectal cancer [77]. Irinotecan may potentiate radiation by attaching to the DNA-topoisomerase I adducts in sites of DNA single strand breaks. Alternatively, fractionated radiotherapy could synchronise the tumour cell population in the S phase of the cell cycle, where cells are more sensitive to irinotecan chemotherapy.

**Clinical studies of chemoradiation with capcitabine in combination with irinotecan**

A phase I study has been conducted to evaluate the combination of capcitabine and irinotecan chemoradiation as preoperative downstaging therapy in 12 patients with LARC [78]. Patients received continuous capcitabine (500, 650 or 800 mg/m² twice daily) plus irinotecan (40 mg/m²/week) plus radiotherapy (total dose 45 Gy). Significant pathological responses have been observed, with downstaging of at least one T-stage in 83% of patients (Table 3). No increases in perioperative or postoperative complications have been reported, with only one patient experiencing grade 3 gastrointestinal adverse events. The MTD has not yet been reached with capcitabine combined with weekly i.v. infusions of irinotecan (40 mg/m²) during pelvic radiotherapy.

A second phase I dose-escalation study [79] is evaluating the recommended dosing regimen of capcitabine 500 mg/m² continuously twice daily plus irinotecan 50 mg/m² on days 1, 8, 15, 22 and 29 with standard radiation. A very low rate of grade 3/4 adverse events have been reported in the 30 patients evaluable to date and the pCR rate is comparable to that reported with infusional 5-FU/irinotecan schedules.

A UK phase I study in 22 patients administered continuous capcitabine with 4-weekly infusions of irinotecan [80]. Recommended doses were capcitabine 825 mg/m² continuously twice daily plus irinotecan 60 mg/m² on days 1, 8, 15 and 22 with pelvic radiation (45 Gy). DLTs were mainly gastrointestinal and neutropenia. Early efficacy data are very promising, with R0 resections in 95% of patients. A confirmatory phase II study is ongoing and these doses should not be used until confirmed.

In another phase I dose-escalation study [81] dose-limiting toxicity has not yet been reached with this regimen, which has

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of evaluable patients</th>
<th>Treatment</th>
<th>Downstaging rate (%)</th>
<th>Response (%)</th>
<th>R0 resections (%)</th>
<th>Grade 3/4 adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kennedy et al. [78]</td>
<td>12</td>
<td>Pelvic RT (total dose 45 Gy) + C (500, 650 or 800 mg b.i.d.) + I (40 mg/m²/week)</td>
<td>83</td>
<td>Clinical ORR (83)</td>
<td>NR</td>
<td>MTD not yet reached. One patient with grade 3 gastrointestinal events</td>
</tr>
<tr>
<td>Willeke et al. [79]</td>
<td>30 (safety)</td>
<td>Pelvic RT (total dose 50.4 Gy) + C (500 mg b.i.d., days 1–38) + I (50 mg/m² days 1, 8, 15, 22, 29 &amp; 36)</td>
<td>NR</td>
<td>pCR (18)</td>
<td>100</td>
<td>Grade 3/4 leucopenia (20%), grade 3 nausea/vomiting (3%), grade 3 transaminase increase (3%), One patient with ventricular fibrillation</td>
</tr>
<tr>
<td>Gollins et al. [80]</td>
<td>22 (safety)</td>
<td>Pelvic RT (total dose 45 Gy) + C (650 or 825 mg/m² b.i.d.) + I (50–70 mg/m²/week) ×5 weeks</td>
<td>74</td>
<td>pCR (26)</td>
<td>95</td>
<td>Grade 3 diarrhoea (9%), anorexia (9%), nausea/vomiting (3%), lethargy (5%). No grade 4 events</td>
</tr>
<tr>
<td>Becerra et al. [81]</td>
<td>12</td>
<td>Pelvic RT (18 Gy Monday–Friday, total dose 450 Gy plus 54 Gy boost) + C (825 mg/m² b.i.d. Monday–Friday) + I (30–50 mg/m²/week)</td>
<td>67</td>
<td>NR</td>
<td>NR</td>
<td>Grade 3: urinary tract infection (8%), infection (colitis, 8%), abdominal cramps (8%), pain (8%). No grade 4 events reported</td>
</tr>
<tr>
<td>Klautek et al. [82]</td>
<td>11 (safety)</td>
<td>Pelvic RT (total dose 50.4 Gy) + C (500, 650 or 825 mg/m² b.i.d.) + I (40 mg/m²/week) ×6 weeks</td>
<td>82</td>
<td>pCR (18)</td>
<td>91</td>
<td>Grade 3/4 diarrhoea (39%), No grade 3 haematological or skin reaction</td>
</tr>
</tbody>
</table>

b.i.d., twice daily; C, capcitabine; DLT, dose-limiting toxicity; I, irinotecan; LV, leucovorin; MTD, maximum tolerated dose; NR, not reached/reported; O, oxaliplatin; ORR, overall response rate; pCR, pathologic complete response; RT, radiotherapy; TME, total mesorectal excision.
been shown to downstage patients at all dose levels tested to date (Table 3). Accrual of patients into the next dose level (irinotecan 60 mg/m²/week) is continuing.

In a slightly larger phase I/II dose-escalation study [82], patients are receiving continuous capcitabine (500, 650 or 825 mg/m² twice daily) plus irinotecan (40 mg/m²/week) plus radiotherapy (total dose 50.4 Gy) for 6 weeks. Of the 23 patients enrolled, 11 have undergone full surgery with an R0 resection rate of 91%, downstaging in 82% of patients and a pCR of 18% (Table 3). Recruitment is ongoing in the phase II portion of the study with patients receiving the recommended dose of capcitabine 750 mg/m² twice daily plus weekly irinotecan 40 mg/m² and concurrent radiation.

Although preliminary, the current findings indicate that combinations of capcitabine and weekly irinotecan are feasible in this setting.

capcitabine/new agent combinations

Phase I/II studies are ongoing/planned to investigate the addition of new biological agents (bevacizumab, cetuximab or gefitinib) to capcitabine-based chemoradiation. Ongoing studies include a Belgium phase I/II trial evaluating capcitabine plus cetuximab and radiotherapy in LARC, with surgery planned 6–8 weeks after chemoradiation. Also ongoing is a US phase II study of capcitabine plus celecoxib, oxaliplatin and radiotherapy in LARC.

Planned trials include an Italian phase II study of capcitabine with bevacizumab and radiotherapy in neoadjuvant colorectal cancer, a phase II study in Serbia-Montenegro evaluating capcitabine with mitomycin-C and radiotherapy in LARC, a UK phase II randomized study of capcitabine plus oxaliplatin followed by capcitabine plus cetuximab and radiotherapy in LARC, followed by adjuvant capcitabine (EXPERT-C), and three US studies evaluating capcitabine with either celecoxib or gefitinib in LARC.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of evaluable patients</th>
<th>Treatment</th>
<th>PCR (%)</th>
<th>R0 resections (%)</th>
<th>Grade 3/4 adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sauer et al. [9]</td>
<td>363</td>
<td>Pelvic RT (1.8 Gy/day, total 50.4 Gy) ×5 weeks + CI 5-FU (1000 mg/m²/day) days 1–5, weeks 1 &amp; 5</td>
<td>6</td>
<td>NR</td>
<td>Diarrhoea (12%), erythema (12%), leukopenia (13%), dermatitis (1%)</td>
</tr>
<tr>
<td>Bosset et al. [10]</td>
<td>400</td>
<td>Pelvic RT (1.8 Gy/day, total 45 Gy) ×5 weeks + bolus 5-FU (350 mg/m²/day) + LV (20 mg/m²/day) days 1–5, weeks 1 &amp; 5</td>
<td>14</td>
<td>NR</td>
<td>Grade 2 (54%), grade 2 diarrhoea (34%), grade 2 dermatitis (26%), grade 2 vomiting (7%)</td>
</tr>
<tr>
<td>Conroy et al. [83]</td>
<td>344</td>
<td>Pelvic RT (1.8 Gy/day, total 45 Gy) ×5 weeks + bolus 5-FU (350 mg/m²/day) + LV (20 mg/m²/day) days 1–5, weeks 1 &amp; 5</td>
<td>10</td>
<td>NR</td>
<td>Overall (14%)</td>
</tr>
<tr>
<td>Bujko et al. [84]</td>
<td>157</td>
<td>Pelvic RT (1.8 Gy/day, total 50.4 Gy) + bolus 5-FU (325 mg/m²/day) + LV (20 mg/m²/day) days 1–5, weeks 1 &amp; 5</td>
<td>16</td>
<td>96</td>
<td>Grade 3/4 overall (18%)</td>
</tr>
<tr>
<td>Roh et al. [85]</td>
<td>130</td>
<td>Pelvic RT (total 50.4 Gy) + bolus 5-FU (325 mg/m²/day) + LV (20 mg/m²/day) days 1–5, weeks 1 &amp; 5</td>
<td>17</td>
<td>NR</td>
<td>Diarrhoea (34%)</td>
</tr>
</tbody>
</table>

CI, continuous infusion; LV, leucovorin; NR, not reached/reported; pCR, pathologic complete response; RT, radiotherapy.

discussion

5-FU-based chemoradiation is currently the recommended standard therapy for patients with stage II/III rectal cancer in the USA and Germany [5, 6]. The recent results of the German CAO/ARO/AIO-94 study [9] are likely to increase the use of preoperative therapy in most of Europe, compared with a general preference for postoperative therapy in the USA.

Pathological complete response following preoperative radiation alone has been reported in 4%–10% of patients. More recently, preoperative radiation has been combined with 5-FU as a radiation sensitiser with the aim of increasing the downstaging of tumours. A variety of chemotherapeutic approaches and radiation schedules have been utilised in single institutional studies and have resulted in a range of pathological complete response rates of 10%–50%. It is interesting to compare pCR rates and grade 3/4 toxicity rates in trials of 5-FU/LV-based chemoradiation versus capcitabine-based chemoradiation in LARC. As might be expected, in most of the randomised trials of 5-FU/LV chemoradiation regimens in LARC [9, 10, 83–85], higher pCR rates are associated with higher rates of grade 3/4 toxicity (Table 4). A number of variables can serve to alter pCR, including the patient population, accuracy of pathologic reporting, dose of radiotherapy used, field size effects, dose intensity of chemotherapeutic used and the use of bolus versus infusional 5-FU. Reporting of treatment-related toxicity is also variable and does not always lend itself to comparisons.

However, in the capcitabine chemoradiation phase II studies listed in Tables 1–3, there does not appear to be any relationship between the dose of radiotherapy, pCR and toxicity. The high pCR rates reported with capcitabine-based chemoradiation in many of the studies do not appear to be associated with higher rates of grade 3/4 toxicity. While the usual limitations of cross-study comparisons and the small size of many of the trials should be taken into account when interpreting these findings, the promising pCR rates and low rate of grade 3/4 toxicity provide support for capcitabine as part of chemoradiation regimens in LARC today.
In view of the robust phase III data comparing capecitabine chemoradiation regimens in patients with LARC, the list below provides our recommendations for using capecitabine plus oxaliplatin in the treatment of patients with metastatic colorectal cancer [60–62], early results suggest that combinations of oxaliplatin and capecitabine chemoradiation are highly effective and also well tolerated in the neoadjuvant treatment of LARC. While fewer data are available, capecitabine-based chemoradiation in combination with weekly irinotecan also appears to be feasible. Ongoing studies will hopefully determine whether these combinations are associated with high enough compliance and acceptable toxicity, and can improve efficacy compared with today’s current standard of care.

In conclusion, the data presented in this review provide a clear rationale for replacing i.v. 5-FU with oral capecitabine in chemoradiation for patients with LARC. The NSABP R04 study, which aims to do this, has recently started to enrol patients. In view of the robust phase III data comparing capecitabine versus 5-FU, as single-agent therapy or in combination both in the metastatic and adjuvant settings, we anticipate that many clinicians will make this change before confirmatory phase III data are available in LARC.

acknowledgements

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references

39. Lin EH, Skibber J, Delcos M et al. A Phase II study of capecitabine and
38. Dunst J, Reese T, Debus J et al. Phase-II-study of preoperative chemoradiation
37. Ngan SY, Michael M, Mackay J et al. A phase I trial of preoperative radiotherapy
36. Dunst J, Reese T, Sutter T et al. Phase I trial evaluating the concurrent
28. Twelves C, Boyer M, Findlay M et al. Capecitabine (Xeloda) improves medical
26. Schüller J, Cassidy J, Dumont E et al. Preferential activation of capecitabine in
22. Van Cutsem E, Hoff PM, Harper P et al. Oral capecitabine vs intravenous 5-
cancer by combining protracted-infusion fluorouracil with radiation therapy
20. Van Cutsem E, Hoff PM, Harper P et al. Oral capecitabine vs intravenous 5-
fluorouracil and leucovorin: integrated efficacy data and novel analyses from two
18. Twelves C, Wong A, Novacki MP et al. Capecitabine as adjuvant treatment for
17. Scheithauer W, McKendrick J, Beggie S et al. Oral capecitabine as an alternative to
i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: safety results of a
16. Schüller J, Cassidy J, Dumont E et al. Preferential activation of capecitabine in
carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours
resource use compared with 5-fluorouracil plus leucovorin in a phase III trial
13. McKendrick JJ, Cassidy J, Chakravee-Sirisuk S et al. Capecitabine (X) is resource
saving compared with i.v. bolus 5-FU/LV in adjuvant chemotherapy for Dukes’ C
colon cancer patients: Medical resource utilization (MRU) data from a large phase
capecitabine in the adjuvant setting. Results from the X-Act trial comparing
phosphorylase and enhances the efficacy of capecitabine (Kalexda) in human
9. Verso M, Agnelli G. Venous thromboembolism associated with long-term use of
8. Clark DR, Raffin TA. Infectious complications of indwelling long-term central venous
6. Dunst J, Reese T, Sutter T et al. Phase I trial evaluating the concurrent
5. Nyan SY, Michael M, Mackay J et al. A phase I trial of preoperative radiotherapy
3. Lin EH, Skibber J, Delcos M et al. A Phase II study of capecitabine and
concomitant boost radiotherapy (XRT) in patients (pts) with locally advanced rectal
2. Shen W, Liu Y, Ma X et al. Capecitabine (X) combined with radiotherapy in
Chinese patients (pts) with advanced or relapsed rectal carcinoma. Proc Am Soc Clin
1. Kocaiova I, Svoboda M, Klicova K et al. Combined therapy of locally advanced


