A phase I dose escalation study of continuous oral capecitabine in combination with oxaliplatin and pelvic radiation (XELOX-RT) in patients with locally advanced rectal cancer

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Received 27 May 2005; revised 1 September 2005; accepted 2 September 2005

Purpose: To determine the maximum tolerated dose (MTD) of continuous oral capecitabine plus oxaliplatin and pre-operative pelvic radiotherapy (XELOX-RT).

Patients and methods: Patients with clinically unresectable rectal cancer or for whom resection with histologically clear (R0) surgical margins was unlikely received continuous capecitabine (500–825 mg/m2 twice daily, 7 days/week), oxaliplatin 2-h intravenous infusion (130 mg/m2 days 1 and 29) and pelvic radiotherapy (Monday–Friday for 5 weeks, total dose 45 Gy in 25 daily 1.8 Gy fractions). The MTD was the capecitabine dose causing dose-limiting toxicities (DLTs; treatment-related grade 3/4 toxicities) in one-third or more of patients treated per dose level.

Results: Eighteen patients received three dose levels. The MTD was capecitabine 825 mg/m2 twice daily; DLTs occurred in two of six patients (grade 3 diarrhoea, rectal pain with local skin reaction). No DLTs occurred in six patients receiving capecitabine 650 mg/m2 twice daily. Grade 3/4 toxicity was rare, with minimal myelosuppression. Although predominantly a dose-finding study, XELOX-RT showed promising activity. Fourteen patients had histologically confirmed R0 resections and five had a pathological complete response.

Conclusions: The recommended dose for further study is capecitabine 650 mg/m2 twice daily with oxaliplatin and radiotherapy. XELOX-RT showed promising antitumour activity. Further evaluation is underway.

Key words: Capecitabine, chemoradiation, locally advanced rectal cancer, oxaliplatin

introduction

Capecitabine (Xeloda®; F. Hoffmann-La Roche Ltd, Basel, Switzerland) is an orally bioavailable fluoropyrimidine with a rapidly expanding role as a substitute for 5-fluorouracil (5-FU) in the treatment of colorectal and other cancers. Capecitabine was rationally designed to generate 5-FU preferentially at the tumour site, via a three-step enzymatic process exploiting the significantly higher activity of thymidine phosphorylase (TP) in tumour tissue compared with healthy tissue [1, 2]. As first-line therapy for metastatic colorectal cancer, capecitabine has demonstrated superior antitumour activity and a favourable safety profile compared with 5-FU/leucovorin (LV) (Mayo Clinic regimen) [3, 4]. The improved activity and safety of capecitabine versus 5-FU/LV (Mayo Clinic regimen) is also mirrored in the adjuvant treatment of colon cancer [5, 6].

Additionally, preclinical studies have demonstrated that radiotherapy further upregulates TP activity in tumour tissue, and that capecitabine in combination with radiotherapy has supra-additive antitumour activity compared with either treatment alone [7]. These findings have provided a rationale for the evaluation of chemoradiation schedules incorporating capecitabine.

While surgery is the mainstay of treatment for stage II and III rectal cancer, historically the disease has been characterised by a high risk of local recurrence and poor survival. Even in the context of modern, meticulous surgical techniques such as total mesorectal excision (TME), 5-year survival rates remain in the range of 40–60% [8, 9]. A recent meta-analysis of randomised controlled trials show pre-operative radiotherapy reduces the rate of locoregional recurrence (P <0.001) and may improve 5-year survival [10]. These data lend support to the use of pre-operative radiotherapy.

Improvements in pre-operative staging through the use of high resolution, thin-slice magnetic resonance imaging (MRI)
allow the identification of patients at high risk of local recurrence (and by inference those likely to have poor overall survival) [11]. For this reason, MRI is being used more commonly to select patients for pre-operative chemoradiation. Currently, in the UK, pre-operative chemoradiation is used selectively, most specifically for patients at risk of having tumour encroaching upon the circumferential resection margin (CRM; as determined by radiological, clinical or other criteria). The CRM involvement is now known to be the strongest risk factor predicting for both local recurrence and indeed overall survival [12, 13].

Other advantages of the pre-operative approach include the treatment of potential micrometastatic disease outside the radiation fields. Significant tumour downstaging may also increase the chance of a sphincter-sparing procedure [14].

Most chemoradiation schedules for locally advanced rectal cancer (LARC) combine pelvic radiation with either continuous infusion 5-FU or 5-FU modulated by LV. More recently, capecitabine has been evaluated in this setting, as a potentially more effective alternative to intravenous 5-FU/LV [15, 16].

The addition of oxaliplatin to 5-FU/LV confers a significant clinical benefit in the treatment of metastatic colorectal cancer [17–19]. In the adjuvant setting, the addition of oxaliplatin to 5-FU/LV significantly improves disease-free survival [20]. Our group previously evaluated the combination of 5-FU/LV with escalating doses of oxaliplatin on day 2 and day 30 of a 5-week course of pre-operative radiotherapy in LARC [21]. The recommended dose of oxaliplatin in this setting was 130 mg/m². In addition, a recent study in 96 patients demonstrated that XELOX (capecitabine 1000 mg/m² days 1–14, plus oxaliplatin 130 mg/m² on day 1, every 21 days) is a highly effective and well-tolerated first-line treatment for metastatic colorectal cancer [22]. This study builds on the data described above and evaluates escalating doses of capecitabine plus oxaliplatin (130 mg/m²) and radiation (XELOX-RT).

patients and methods

This is a phase I, dose-escalation study of capecitabine administered in combination with oxaliplatin and pelvic radiotherapy in patients with rectal cancer. It was conducted at five UK centres in accordance with the International Good Practice principles and local ethics and regulatory requirements. All patients provided written informed consent prior to study-specific screening procedures.

The primary objective was to determine the maximum tolerated dose (MTD) of continuous oral capecitabine, administered twice daily, 7 days for 5 weeks, in combination with oxaliplatin 130 mg/m², on days 1 and 29, and standard pre-operative pelvic radiotherapy in patients with primary unresectable rectal cancer. Secondary objectives included determination of safety profile, compliance and preliminary efficacy of the regimen. The latter was reflected in the proportion of patients undergoing histologically confirmed complete resection at all surgical margins [R0 (CRM negative)].

criteria

Patients with biopsy-proven LARC were included in the study. Patients were selected either on the basis of tumour fixity on digital rectal examination or a high likelihood of CRM involvement, as indicated by MRI. Tumours were classified as rectal if the lower limit was located within 12 cm of the anal verge on rigid sigmoidoscopy. Clinical staging was based on the criteria from the American Joint Committee on Cancer (2002) [23]. Patients were aged between 18 and 75 years and had Eastern Cooperative Oncology Group performance status 0 to 1. Adequate haematological and renal function (absolute neutrophil count >21000/μL, and serum creatinine ≤1.25 upper normal limit) were also required. Patients should have no evidence of metastatic disease based on computed tomography scanning or chest X-ray and liver ultrasound.

Exclusion criteria included prior chemotherapy and/or pelvic radiation, tumour recurrence after primary surgery, or evidence of metastatic disease. Patients with more than six stools per day were also excluded, as it was felt that this would preclude accurate grading of toxicity. Patients were ineligible if there was a large amount of small bowel in the radiation field (>500 ml in the high-dose volume). In addition, sexually active patients unwilling to practice effective contraception were also excluded. Other exclusion criteria were pregnancy, inflammatory bowel disease and cardiac conditions that would compromise the safe delivery of capecitabine.

treatment

Three groups of six patients received twice-daily capecitabine doses of 500 mg/m² (dose level 1), 650 mg/m² (dose level 2) or 825 mg/m² (dose level 3). Oxaliplatin 130 mg/m² was delivered as a 2-h infusion on days 1 and 29. In the event of arm pain or laryngeal dysaesthesia, the duration of the second infusion was lengthened to 4 h.

Patients received pre-operative pelvic radiotherapy (45 Gy was delivered in daily 1.8 Gy fractions) in a prone position with a full bladder. Using information from clinical examination and pelvic MRI, the gross tumour volume (GTV) was defined using a computed tomography planning scan. The planning target volume was derived by growth of 2–3 cm around the GTV according to protocol-defined radiation planning diagrams. The posterior border was, however, fixed on the most posterior aspect of the bony sacrum. Mega-voltage radiotherapy was delivered using a three- or four-field box technique. The protocol accepted a more modest margin superiorly, if necessary, to maintain the superior border and the extent of the field within the L5/S1 junction, and therefore reduce bowel toxicity. Opaquification of the small bowel was recommended.

dose-limiting toxicities

Adverse events were classified according to the National Cancer Institute common toxicity criteria, version 2 (30 April 1999). Dose-limiting toxicities (DLTs) included any grade 3 or 4 non-haematological or clinical adverse event (except alopecia), grade 4 neutropenia or grade 3/4 neutropenia with fever requiring supportive therapy, and hyperbilirubinaemia. Any adverse event requiring capecitabine interruption for more than seven doses or more than 10% of the planned dose was also considered dose limiting. Brief gastrointestinal toxicity that reduced to grade 2 within 2 days, and which did not require omission of more than seven doses (or more than 10% of the planned dose) of capecitabine was not considered dose limiting.

dose escalation scheme

The MTD was defined as the capecitabine dose at which two or more of the six patients experienced a DLT. If no more than one of the six patients experienced a DLT, capecitabine dose escalation was permitted, within the subsequent group. No intrapatient dose escalation was permitted. The dose level preceding the MTD was identified as the recommended capecitabine dose for phase II evaluation.

patient and tumour evaluation

Patients were evaluated at baseline and underwent weekly clinical assessment during weeks 1–10, followed by assessments at months 3, 6 and 12. Evaluations included a complete clinical examination, and a complete blood
count and blood chemistry analysis. Safety was monitored continuously until the end of week 10.

Assessment of R0 (CRM negative) resectability was evaluated using MRI (unless contra-indicated) on day 75 (±7 days). The protocol recommended that definitive surgery should be planned a minimum of 6 weeks following completion of chemoradiation.

Histopathologic examination of the resected specimen was performed according to the technique described by Quirke et al. [24]. R0 resection was defined by a CRM >1 mm.

results

patient characteristics

Between July 2001 and October 2002, a total of 18 patients were recruited to this phase I study. Patient demographics and baseline disease characteristics are shown in Table 1. The patient population comprised 12 men and six women with a median age of 57 years (range 37–71).

DLTs and recommended dose level

There were no DLTs in patients treated at dose levels 1 and 2. At dose level 3 (capecitabine 825 mg/m² twice daily), one patient developed grade 3 diarrhoea in week 9, following a full course of XELOX-RT therapy. This patient had previously experienced diarrhoea unrelated to treatment, grade 1/2 paraesthesia and nausea and grade 1 vomiting. Treatment was modified for this patient and the diarrhoea resolved. A second patient at this dose level experienced grade 3 rectal pain associated with a grade 3 radiation skin reaction that required capecitabine treatment interruption for more than seven doses. Dose escalation was therefore stopped at capecitabine 825 mg/m², which was identified as the protocol-defined MTD. Two further grade 3/4 adverse events at this dose level (another case of grade 3 diarrhoea and a case of grade 3/4 lethargy) were not defined as DLTs according to the protocol criteria. Capecitabine 650 mg/m² twice daily (evaluated as dose level two) was identified as the recommended dose for further phase II evaluation in combination with oxaliplatin 130 mg/m², days 1 and 29, and pelvic radiotherapy.

other adverse events

Table 2 lists the most common (>15% of patients) clinical adverse events and laboratory abnormalities experienced by patients treated at each dose level. Overall, acute neurotoxicity was the most frequent adverse event, occurring in 16 patients (89%); however, it was reversible in all patients. The next most frequent toxicity was gastrointestinal, with diarrhoea reported in 12 patients (67%). In contrast to other capecitabine chemoradiation studies in which grade 3 hand–foot syndrome was the main DLT [25], this side-effect was observed in only two patients and was of only grade 1 intensity in both cases. Grade 3/4 adverse events were infrequent, with only one grade 3/4 event observed in patients treated at the first and second dose levels. The regimen was not associated with significant myelosuppression, and no grade 3/4 neutropenia or
thrombocytopenia were encountered. One patient being treated at dose level 3 died as a result of a pre-operative cerebrovascular accident. All fluoropyrimidine-based treatment appears to be associated with a slightly increased risk of thrombotic events.

**compliance**

There was full compliance (no reduction in planned dose or duration of treatment) with radiation therapy in patients treated at dose level 1, and only one patient required a protocol-directed chemotherapy dose reduction for grade 2 diarrhea. Of the six patients treated at dose level 3, three required a chemotherapy dose reduction; of these three, two also required interruptions of radiation. The chemotherapy dose modifications occurred in both patients with DLTs, and in the patient who experienced a cerebrovascular accident. Notably, there was full compliance with radiotherapy and chemotherapy for the six patients treated at dose level two (recommended dose). Postoperative problems with minor radiologic anastomotic leaks appeared no worse than anticipated for patients undergoing this form of treatment before resection, and there were no postoperative deaths.

**response to treatment**

Seventeen patients were reassessed 6 weeks after treatment and, based on the clinical findings, either underwent surgery immediately, or had their surgery postponed until further downsizing was evident.

Of the 18 patients treated with XELOX-RT, 16 underwent surgery. One patient died as a result of a pre-operative cerebrovascular accident, and one patient was considered inappropriate for resection due to the presence of liver metastases on restaging. Fourteen of the 16 patients underwent an R0 (CRM negative) resection. CRM encroachment to within 1 mm was documented in the remaining two patients (one of whom had a T4 tumour at baseline). Abdomino-perineal excision was performed in 28% (five patients). Exenterative surgery was not required in any patient.

Tumour downstaging was defined by a comparison of clinical TN stage prior to treatment (as determined by pelvic MRI) with histopathologic stage post-surgery. Reduction of tumour stage was observed in 13 patients (72%), and pathological complete responses (pCRs) occurred in five patients (38% of the downstaged group; 28% of all evaluable patients). Of the five patients achieving a pCR, three were treated at dose level 1 (capecitabine 500 mg/m²), one was treated at dose level 2 (capecitabine 650 mg/m²) and one was treated at dose level 3 (capecitabine 825 mg/m²). None of the patients experienced disease progression within the pelvis. Positive lymph nodes were found in only two patients, compared with 10 patients predicted at baseline.

**discussion**

The long-term outcome following treatment for LARC remains poor. The results of the Intergroup 0114 study of post-operative chemoradiation in rectal cancer demonstrated 5-year disease-free and overall survival rates of 44% and 55%, respectively, for patients with T3N+/T4 tumours [26].

The use of more meticulous surgical resection techniques produces improved rates of long-term tumour control [27], probably through increasing the proportion of patients able to undergo a curative resection (R0 with a negative CRM), i.e. with tumour extending <1 mm from the surgical CRM. A negative CRM is now known to be a highly relevant prognostic factor [12, 13, 24, 28]. Improved techniques of pre-operative imaging can identify patients at risk of an involved margin resection, and thereby allow this group of patients to be selected for preoperative treatment. Pre-operative therapy is routinely used in some large American institutions [29, 30], and there is growing interest in achieving tumour downstaging and subsequent curative R0 resection and sphincter-sparing procedures.

Capecitabine chemoradiation has been extensively evaluated in patients with LARC [25, 31–39]. Single-agent phase I studies identified a recommended dose of capecitabine 825 mg/m², administered twice daily without interruption, plus standard radiotherapy for neo-adjuvant treatment of rectal cancer [25]. Phase II evaluation of the recommended regimen has confirmed the high efficacy and favourable safety profile [15, 16]. Chemoradiation incorporating capecitabine in place of infusional 5-FU is more convenient, with potential to enhance quality of life and reduce medical resource use. Based on this strong rationale, the National Surgical Adjuvant Breast and Bowel Project (NSABP) is evaluating neo-adjuvant, capecitabine-based chemoradiation in a randomised, phase III trial (NSABP R-04) [40]. Based on such studies, twice-daily doses of capecitabine ranging from 500 to 825 mg/m² were selected for study in the present trial. The favourable tolerability and high efficacy of the XELOX combination in patients with metastatic disease suggests an opportunity to further improve the efficacy of chemoradiation [22]. A previous study from this group using 5-FU, folinic acid and oxaliplatin has suggested doses of 130 mg/m² to be deliverable on days 2 and 30 [21]. In the study we now report, in patients undergoing pre-operative radiotherapy, with 45 Gy delivered to the pelvis in 25 fractions of 1.8 Gy and who receive oxaliplatin at 130 mg/m², a continuous capecitabine dose of 825 mg/m² twice daily is the MTD. At this dose, patients experienced DLTs of diarrhea and rectal pain. A dose of 650 mg/m² is therefore recommended for phase II study.

As expected, mild to moderate acute neurotoxicity (a side-effect characteristic of oxaliplatin) was the most common adverse event observed with XELOX-RT, although this did not affect compliance, and was short-lived. Predictably, gastrointestinal side-effects were also common, with diarrhea identified as a predominant adverse event and a DLT due to both chemotherapy and radiation. Notably, hand–foot syndrome, a common toxicity associated with capecitabine, was observed in only two patients and was limited to grade 1 intensity in both cases. No grade 3/4 events occurred in patients treated at the recommended dose (capecitabine 650 mg/m²).

In metastatic colorectal cancer, capecitabine has a favourable safety profile with minimal myelosuppression, and oxaliplatin is also well tolerated. It is therefore unsurprising that myelosuppression was particularly rare and that neither grade 3/4 neutropenia nor leucopenia was observed. The favourable tolerability of XELOX-RT contributed to good compliance, with no reduction in planned dose or duration of treatment.
Roedel et al. [47] (PROCTFUL [48]) showed that capecitabine (750 mg/m² twice daily, days 1–5 every week) combined with oxaliplatin (60 mg/m², weekly) and radiotherapy (50.4 Gy total dose) has demonstrated consistently high activity in the neo-adjuvant setting. The complete pathologic response rate of 25% to 29% in phase I/II trials [44–46]. Three other studies have evaluated XELOX regimens in neo-adjuvant chemoradiation. In a recent German phase I/II study, capecitabine was administered on days 1–14 and 22–35 in combination with oxaliplatin and radiotherapy [47]. The study identified a recommended dose of twice-daily capecitabine 825 mg/m², oxaliplatin 50 mg/m² (days 1, 8, 22 and 29) and radiotherapy (50.4 Gy total dose). The dose intensities of capecitabine and radiotherapy were similar in the Roedel et al. [47] study compared with the current study (1320 mg/m² per day versus 1300 mg/m² per day over 5 weeks and 50.4 Gy versus 45 Gy, respectively). The complete pathologic response rates were also similar in the two studies (19% versus 28%), as was the R0 resection rate (94% and 88% for the German and current study, respectively) (Table 3). These data suggest that, in combination with oxaliplatin and radiotherapy, a capecitabine dose intensity of ~650 mg/m² twice daily over 5 weeks is deliverable, with modest, manageable toxicity.

Preliminary data from the phase II, PROCTFUL study (n = 16) [48] showed that capecitabine (750 mg/m² twice daily, days 1–5 every week) combined with oxaliplatin (60 mg/m², weekly) and radiotherapy is also an effective neo-adjuvant treatment. The dose intensity of capecitabine is reduced compared with this trial (1071 versus 1300 mg/m²), but the dose intensity of oxaliplatin is increased (8.57 versus 7.4 mg/m²). All patients receiving capecitabine, oxaliplatin and radiotherapy have undergone R0 resection, and complete pathologic response was observed in four patients (25%), although no patients were downstaged to pT1/2N0. Interestingly, the PROCTFUL regimen was not as well tolerated as the recommended dose evaluated in this study, possibly because of increased oxaliplatin dose intensities. Grade 3/4 toxicities included two cases of tenesmus, and one case each of diarrhoea, anaemia and urinary frequency.

The CORE study is evaluating a third capecitabine and oxaliplatin chemoradiation regimen. This phase II study is evaluating a Monday to Friday schedule of capecitabine (850 mg/m² twice daily) with weekly oxaliplatin (50 mg/m²) and radiotherapy in patients with LARC (D. Sebag-Montefiore, personal communication). Patients are selected on MRI criteria, which make a curative resection unlikely with surgery alone. This study also mandates rigorous quality assurance for TME surgery, radiotherapy and pathologic reporting of a complete histopathologic response.

The oral administration of capecitabine avoids problems associated with coordinating hospital-based administration of intravenous chemotherapy with radiation. In both the Roedel et al. [47] and PROCTFUL [48] studies, oxaliplatin is administered weekly, whereas the regimen evaluated in the present study only requires one visit for oxaliplatin administration every 4 weeks, which may be more convenient for both the patient and clinic. The oral administration of capecitabine also avoids potential problems associated with central venous catheters that are required for the administration of 5-FU, such as deep vein thrombosis, infection and localised pain.

It seems likely that further improvements in overall survival will be achieved by reducing the incidence of metastatic disease, and it is anticipated that an effective neo-adjuvant chemoradiation regimen may be the key to improved clinical outcomes in LARC. The therapeutic advantages of a fluoropyrimidine–oxaliplatin combination recently demonstrated amongst colon cancer patients in the adjuvant setting lend support to further evaluation of this XELOX–RT regimen for neo-adjuvant treatment of patients with LARC [20]. Indeed, a multicentre phase II study treating 80 patients at the recommended dose of XELOX–RT from this trial (capecitabine 650 mg/m², oxaliplatin 130 mg/m² and radiotherapy 45 Gy) has recently been completed [49].

Table 3. XELOX–RT regimens demonstrate consistently high activity in the neo-adjuvant setting

<table>
<thead>
<tr>
<th>Study</th>
<th>Capecitabine dose intensitya (mg/m² per day)</th>
<th>Oxaliplatin dose intensitya (mg/m² per day)</th>
<th>pCR (%)</th>
<th>pT1/2N0 (%)</th>
<th>R0 resections (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROCTFUL [48] (n = 16)</td>
<td>1071</td>
<td>8.57</td>
<td>25</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Roedel et al. [47] (n = 31)</td>
<td>1320</td>
<td>7.14</td>
<td>19</td>
<td>23</td>
<td>94</td>
</tr>
<tr>
<td>Current XELOX–RT regimen (n = 18)</td>
<td>1300</td>
<td>7.4</td>
<td>28</td>
<td>19</td>
<td>78</td>
</tr>
</tbody>
</table>

aDose intensities show planned dose administered per day over the planned treatment period.

pCR, pathological complete response.

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acknowledgements

We would like to acknowledge the surgeons who collaborated in this study: Mr S. Ambrose, Mr D. Burke, Mr C. E. Elton, Mr J. Griffiths, Mr R. A. Harrison, Mr J. I. Livingstone, Dr A. Melcher, Mr I. C. Mitchell, Mr A. G. Radcliffe, Mr B. R. Rees, Mr P. Sagar, Mr J. Torkingtons, Ms M. Wallace. The authors would also like to thank Dr C. Kennerley for her assistance in drafting the manuscript. Dr Kennerley is a medical writer with Thomson Gardiner-Caldwell Communications. The
Annals of Oncology

authors are grateful for study support from Roche Products Limited.

references


38. Chau I, Cunningham D, Tait D et al. Twelve weeks of neoadjuvant capcitabine (cap) and oxaliplatin (ox) followed by synchronous chemoradiation (CRT) and total mesorectal excision (TME) in MR1 defined poor risk locally advanced rectal cancer resulted in promising tumour regression and rapid symptomatic relief. Proc Am Soc Clin Oncol 2003; 22: 277 (Abstr 1087).
