Oxaliplatin/capecitabine vs oxaliplatin/infusional 5-FU in advanced colorectal cancer: the MRC COIN trial

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BACKGROUND: COIN compared first-line continuous chemotherapy with the same chemotherapy given intermittently or with cetuximab in advanced colorectal cancer (aCRC). Methods: Choice between oxaliplatin/capecitabine (OxCap) and oxaliplatin/leucovorin (LV)/infusional 5-FU (OxFU) was by physician and patient choice and switching regimen was allowed. We compared OxCap with OxFU and OxCap + cetuximab with OxFU + cetuximab retrospectively in patients and examined efficacy, toxicity profiles and the effect of mild renal impairment.

RESULTS: In total, 64% of 2397 patients received OxCap(± cetuximab). Overall survival, progression free survival and overall response rate were similar between OxCap and OxFU but rate of radical surgeries was higher for OxFU. Progression free survival was longer for OxFU + cetuximab compared with OxCap + cetuximab but other efficacy measures were similar. Oxaliplatin/LV/infusional 5-FU (± cetuximab) was associated with more mucositis and infection whereas OxCap(± cetuximab) caused more gastrointestinal toxicities and palmar-plantar erythema. In total, 118 patients switched regimen, mainly due to toxicity; only 16% came off their second regimen due to intolerance. Patients with creatinine clearance (CrCl) 50–80 ml min⁻¹ on OxCap(± cetuximab) or OxFU + cetuximab had more dose modifications than those with better renal function.

CONCLUSIONS: Overall, OxFU and OxCap are equally effective in treating aCRC. However, the toxicity profiles differ and switching from one regimen to the other for poor tolerance is a reasonable option. Patients with CrCl 50–80 ml min⁻¹ on both regimens require close toxicity monitoring.

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Intravenous (IV) 5-FU has been the backbone of treatment for advanced colorectal cancer (aCRC) for over 40 years. Currently capecitabine, an oral fluoropyrimidine (Fp) prodrug, is commonly used as a convenient and effective alternative.

Two large phase III randomised trials compared capecitabine 1250 mg m⁻² twice daily for 14 days repeated every 3 weeks to the Mayo Clinic regimen (Mayo) of IV leucovorin (LV) 20 mg m⁻² followed by daily bolus 5-FU 425 mg m⁻² for 5 days repeated every 4 weeks. Integrated data analysis of the two trials has shown similar overall survival (OS) and progression free survival (PFS) between the two regimens (Van Cutsem et al, 2004). In comparison with Mayo, capecitabine appeared to have a better toxicity profile and to be a safer treatment option for patients with moderate renal impairment. It was also shown that the standard starting dose of capecitabine was safe for patients with mild renal impairment; however, it was recommended that such patients should be monitored closely with prompt treatment interruption and dose reduction in the event of a grade 2 or higher toxicity (Cassidy et al, 2002).

Bolus 5-FU has largely been replaced with a continuous infusion in current treatment regimens. The de Gramont (LV5FU2) regimen of LV/infusional 5FU was compared with Mayo in a randomised trial. LV5FU2 was not only less toxic but was also associated with a better response rate (RR) and PFS (de Gramont et al, 1997).

Oxaliplatin is used in combination with either 5-FU (OxFU) or capecitabine (OxCap). Several phase III studies have compared OxFU with OxCap as first-line treatment for aCRC including: the German AIO (Porschen et al, 2007), the Spanish TTD (Diaz-Rubio et al, 2007), the international NO16966 (Cassidy et al, 2008) and the French FNCLCC (Dureux et al, 2011). All four of these trials, together with two smaller ones, were included in a meta-analysis that showed similar PFS and OS but an inferior overall RR (ORR) for OxCap. Thrombocytopenia, diarrhoea and palmar-plantar erythema (PPE) were more prominent with OxCap-based regimens whereas neutropenia was more prominent with OxFU (Arkenau et al, 2008).

COIN is a three-arm multi-centre phase III open-label randomised controlled trial of the MRC, London. It compared standard continuous chemotherapy with OxFU or OxCap (Arm A)
to each of two experimental arms: same chemotherapy plus cetuximab (Arm B) or intermittent chemotherapy without cetuximab (Arm C). The choice between OxFU and OxCap was nonrandomised but was agreed between the patient and treating clinician before randomisation. COIN did not meet either of its primary outcome measures as the addition of cetuximab was not associated with an improvement in efficacy (Maughan et al, 2011), and intermittent chemotherapy was not confirmed to be noninferior to continuous treatment (Adams et al, 2011).

We report a retrospective analysis comparing OxCap with OxFU and OxCap + cetuximab with OxFU + cetuximab in terms of efficacy and severe side effects. We also examine the success of switching from one OxFp regimen to the alternate as a strategy for keeping patients on first-line treatment in case of intolerance to the first regimen chosen. Following the recommendation from Cassidy et al (2002) to monitor patients with mild renal impairment, we investigate the effect of renal impairment on toxicity on both OxFp regimens. None of these analyses were pre-specified in the COIN trial protocol.

MATERIALS AND METHODS

Patients

Accrual took place in 110 centres in the United Kingdom and the Republic of Ireland between March 2005 and May 2008. Patients (age ≥18) had: measurable metastatic or locally advanced colorectal adenocarcinoma; no previous chemotherapy for advanced disease; WHO performance status (PS) 0–2; adequate bone marrow, liver and kidney function. Patients were excluded if they had: CrCl 50 ml min⁻¹; brain metastases; prior adjuvant treatment with oxaliplatin; uncontrolled medical co-morbidity; or were being considered for liver metastasectomy after initial downstaging chemotherapy.

Treatment plan

OxCap was given as per the XELOX regimen (3-weekly cycles of IV oxaliplatin 130 mg m⁻² over 2 h on day 1 followed by capcitabine 1000 mg m⁻² b.i.d. for 2 weeks). An analysis of the toxicity profile of the regimens after 800 patients had been randomised to the trial showed that the rate of severe diarrhoea for OxCap + cetuximab was excessive at 30% (Adams et al, 2009). Therefore, a protocol amendment in July 2007 mandated that the capcitabine dose in Arm B be reduced from 1000 to 850 mg m⁻² b.i.d. for all future trial patients. Those already on trial had the choice to remain on the higher dose if well tolerated.

OxFU was a 2-weekly regimen of IV LV 175 or nLV-LV 350 mg given concurrently with oxaliplatin 85 mg m⁻² over 2 h on day 1, followed by IV bolus 5-FU 400 mg m⁻² and finally 5-FU 2400 mg m⁻² infused over 46 h. This regimen requires an indwelling venous line (IVL) and is referred to as OxMdG in the United Kingdom. Switching from one regimen to another was allowed for toxicity, compliance, logistics or patient’s choice. All patients switching from OxFU to OxCap had their dose of capcitabine reduced to 850 mg m⁻² in the first cycle as the retained intracellular LV can potentially increase capcitabine toxicity (Hennig et al, 2008).

In Arm B, cetuximab was given in a loading dose of 400 mg m⁻² IV over 2 h on day 1 and subsequently at 250 mg m⁻² over 1 h once a week.

Response was assessed every 12 weeks using the RECIST 1.0 criteria. In both Arms A and B, treatment was continued until disease progression, unacceptable toxicities or patient’s choice. In Arm C, treatment was stopped after 12 weeks and patients with responding or stable disease had a break from chemotherapy but this was restarted on evidence of clinical or radiological disease progression. An unlimited number of 12 week courses were allowed until evidence of treatment failure, which is defined as disease progression on or shortly after stopping treatment.

Renal function

Patients were required to have a baseline CrCl ≥50 ml min⁻¹ as estimated using the Cockcroft and Gault formula (Cockcroft and Gault, 1976). For the purpose of this analysis patients were divided into two CrCl groups: >80 and 50–80 ml min⁻¹ corresponding to normal renal function and mild renal impairment, respectively. This is in line with the study by Cassidy et al (2002) in which the lower cut points for mild renal impairment and normal renal function were set at 51 and 81 ml min⁻¹, respectively.

Efficacy outcome measures

The following outcome measures were compared: OS, PFS and RR at 12 weeks, ORR, and rate of radical surgeries (RRS). Overall RR is defined as the proportion of patients who had PR or CR while on treatment. Rate of radical surgeries is defined as the proportion of patients who had surgery to remove metastatic and/or primary disease with curative intent after starting trial treatment.

Toxicity

Toxicities were graded according to an increasing severity scale of 1–5 based on the NCI Common Terminology Criteria for Adverse Events v3.0. We compared the following ‘grade 3 or worse’ (G3 + ) toxicities between the two regimens: nausea, vomiting, diarrhoea, mucositis, lethargy, PPE, neuropathy, thrombocytopenia, neutropenia and treatment-related infection. The latter was defined as infection with G3/4 neutropenia or any IVL-related infection. Also, we compared rates of dose modification (reductions and delays) in the first 12 weeks of treatment.

Statistics

Arms A and C were combined for all analyses except PFS given the intermittent nature of treatment in Arm C. Comparisons were also made separately in each of Arms A, B and C. However, when looking at reasons for switching from one regimen to another, patients across all arms were combined to maximise power.

Patients were classified according to the chemotherapy regimen (OxCap or OxFU) used in their first cycle. Those who did not receive any trial treatment were excluded from all analyses and those who switched regimen were included in toxicity analyses for toxicities of the first regimen, but were excluded from all efficacy analyses.

OxCap was regarded as the control group for HR and OR calculations. Pearson’s χ² tests were used to calculate P-values, and for cells with low count (n < 5) Fisher’s exact test was used instead; P-values <0.05 were considered significant. Survival curves were plotted using the Kaplan–Meier method. Unadjusted and stratified HR was estimated using the Peto log-rank method, and OR using the Mantel–Haenszel method. For adjusted HR and OR, Cox and logistic regressions were used, respectively.

Efficacy and toxicity outcome measures were corrected for predefined prognostic factors (PFs), and whenever arms were combined correction was also made for trial arm membership.

Prognostic factors (PFs)

Prognostic factors for efficacy outcome measures were determined using a backward stepwise selection procedure, and was carried out separately for OS, PFS and ORR. There was a considerable overlap in PFs for each of these outcome measures. Therefore, the final set of PFs included those that appeared for any of the three
outcomes: sex, white blood cell count, alkaline phosphatase level, the presence of tumour mutation in KRAS, BRAF or NRAS (all wild-type vs any mutant gene), WHO PS (0/1 vs 2), number of metastatic sites (0/1 vs 2) and synchronous vs metachronous metastases. Data on tumour mutation status were missing for some patients. To minimise the resulting loss of statistical power, multiple imputation was used when fitting models entering mutation status (Rubin, 1987). Where the outcome was time-to-event, the Nelson–Aalen estimator and event indicator were entered into the imputation model as suggested by White and Royston (2009). Both adjusted and unadjusted comparisons for efficacy outcome measures are presented hereafter.

PFs for toxicity were determined through the same procedure using the outcome ‘any G3 + toxicity vs none’. These were as follows: CrCl, age and WHO PS.

RESULTS
Patients
See consort diagram (Figure 1). A total of 2445 patients were accrued between 2005 and 2008, of whom 2397 patients received at least one cycle of treatment. In all, 64% of patients received OxCap (± cetuximab) and 36% OxFU (± cetuximab). Tumour mutation status was unknown for 20% of patients. Baseline characteristics of at least one cycle of treatment. In all, 64% of patients received OxCap (± cetuximab) and 36% OxFU (± cetuximab). Tumour mutation status was unknown for 20% of patients. Baseline characteristics of patients on OxCap (± cetuximab) and OxFU (± cetuximab), respectively. Reasons for switching regime were (% out of patients who switched): IVL complications 0 (0%) and 42 (71%), toxicity (not further specified by centres) 45 (76%) and 6 (10%), and patient’s choice or compliance issues 13 (22%) and 10 (17%) of patients on OxCap (± cetuximab) and OxFU (± cetuximab), respectively; the reason was unknown for 1 patient in each group (2%). χ² test for difference in distribution of reasons = 72.2 on 2 degrees of freedom; P < 0.001.

Although all patients who switched from OxCap (± cetuximab) remained on OxFU (± cetuximab) until they came off trial, 13 (22%) of those who switched from OxFU (± cetuximab) later returned to their original regimen after receiving, on average, two OxCap cycles. In most cases this was a temporary measure after the IVL was removed, due to a complication, to avoid treatment delays or the need for IVL re-insertion when patients in Arm C were about to go on a treatment break.

There was no excess of intolerance to the second regimen in patients who switched regimen once: 17 patients (16%) out of this group came off trial due to toxicity or patient’s choice compared with 436 (19%) of those who never switched (P = 0.45).

Efficacy
Survival Overall, 2279 patients were included in the efficacy analyses after excluding those who switched regimen (Table 2 and Figures 2 and 3). Overall survival was similar for OxCap and OxFU with a median of 15.4 and 14.9 months, respectively; adjusted HR 0.92 (0.78, 1.09). Also, there was no difference in PFS: 7.4 and 8.8 months, respectively; adjusted HR 0.90 (0.77, 1.06).

OS was similar between OxCap + cetuximab and OxFU + cetuximab but PFS was longer for OxFU + cetuximab at 8.5 months when compared with OxCap + cetuximab: adjusted HR

Figure 1  CONSORT diagram.

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**Table 1** Baseline characteristics: OxCap vs OxFU

| Regimen                  | Arm A | Arm B (+ cetuximab) | Arm C | Total |
|--------------------------|-------|----------------------|-------|-------|
| **Total N patients**     | 525   | 523                  | 527   | 1575  |
| **Sex**                  |       |                      |       |       |
| Female                   | 187 (36%) | 168 (32%)    | 181 (34%) | 536 (34%) |
| Age                      |       |                      |       |       |
| 65+                      | 239 (46%) | 241 (46%)    | 255 (48%) | 735 (47%) |
| Median age (IQR)         | 63 (56, 69) | 64 (58, 70)    | 64 (57, 70) | 64 (57, 70) |
| WHO PS                   |       |                      |       |       |
| 2+                       | 34 (6%) | 37 (7%)        | 37 (7%) | 108 (7%) |
| Current status of primary tumour |       |                      |       |       |
| Resected                 | 290 (55%) | 269 (51%)    | 261 (50%) | 820 (52%) |
| Site of primary tumour   |       |                      |       |       |
| Colon                    | 287 (55%) | 284 (54%)    | 272 (52%) | 843 (53%) |
| Rectum                   | 162 (31%) | 167 (32%)    | 168 (32%) | 497 (32%) |
| Rectosigmoid junction    | 75 (14%) | 72 (14%)     | 86 (16%) | 233 (15%) |
| Liver                    | 108 (21%) | 122 (23%)    | 102 (19%) | 332 (21%) |
| Liver only               | 389 (74%) | 389 (74%)    | 389 (74%) | 1167 (74%) |
| Lung                     | 206 (39%) | 218 (42%)    | 219 (42%) | 643 (41%) |
| Other (including nodes and peritoneum) | 329 (63%) | 301 (58%)    | 325 (62%) | 955 (61%) |
| Mean number of metastatic sites | 1.93  | 1.88         | 1.95  | 1.92 |
| **Type of metastases**   |       |                      |       |       |
| Colon                    | 287 (55%) | 284 (54%)    | 272 (52%) | 843 (53%) |
| Rectum                   | 162 (31%) | 167 (32%)    | 168 (32%) | 497 (32%) |
| Rectosigmoid junction    | 75 (14%) | 72 (14%)     | 86 (16%) | 233 (15%) |
| Liver                    | 108 (21%) | 122 (23%)    | 102 (19%) | 332 (21%) |
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| Mean number of metastatic sites | 1.93  | 1.88         | 1.95  | 1.92 |
| **Site of primary tumour** |       |                      |       |       |
| Colon                    | 287 (55%) | 284 (54%)    | 272 (52%) | 843 (53%) |
| Rectum                   | 162 (31%) | 167 (32%)    | 168 (32%) | 497 (32%) |
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| Other (including nodes and peritoneum) | 329 (63%) | 301 (58%)    | 325 (62%) | 955 (61%) |
| Mean number of metastatic sites | 1.93  | 1.88         | 1.95  | 1.92 |
| **Cg1 groups**           |       |                      |       |       |
| Normal (≥80 ml min⁻¹)    | 265 (50%) | 268 (51%)    | 272 (52%) | 805 (51%) |
| Impaired (<50–80 ml min⁻¹) | 257 (49%) | 247 (47%)    | 252 (48%) | 756 (48%) |
| Other (<50 or missing)   | 3 (1%) | 8 (2%)        | 3 (1%)  | 14 (1%) |
| **Second-line therapy**  |       |                      |       |       |
| Eligible                 | 477 (91%) | 452 (86%)    | 436 (83%) | 1365 (87%) |
| Chemotherapy             | 278 (58%) | 242 (54%)    | 217 (50%) | 737 (54%) |
| Biological               | 29 (6%) | 26 (6%)      | 23 (5%)  | 78 (6%) |
| Total dose of oxaliplatin (mg) | 797 (464, 1035) | 848 (498, 1023) | 806 (486, 1018) | 528 (454, 1003) |

Abbreviations: Cg1 = creatinine clearance; OxCap = oxaliplatin/capecitabine; OxFU = oxaliplatin/leucovorin (LV)/infusional 5-FU; PS = performance status. *Patients within the sample used throughout this analysis) were considered eligible for second-line therapy if they had come off trial and were not lost to follow-up. Loss to follow-up was defined as no data being received within 6 months of data freeze. Rates of chemotherapy and biologicals received are with respect to numbers eligible.
Table 2  Efficacy outcome measures: OxCap vs OxFU

| Outcome measure | Subgroup       | Median survival (months) | Measure of association (unadjusted) | Measure of association (adjusted*) |
|-----------------|----------------|--------------------------|-------------------------------------|----------------------------------|
| OS              | Arms A and C   | 15.4                     | 1.02 (0.90, 1.15) HR                 | 0.92 (0.78, 1.09)                 |
|                 | Arm A          | 16.0                     | 1.00 (0.84, 1.19) HR                 | 0.95 (0.80, 1.14)                 |
|                 | Arm B          | 15.0                     | 1.01 (0.86, 1.20) HR                 | 0.94 (0.79, 1.12)                 |
|                 | Arm C          | 13.8                     | 1.03 (0.87, 1.23) HR                 | 1.05 (0.86, 1.25)                 |
| PFS             | Arm A          | 7.4                      | 0.93 (0.79, 1.08) ORR                | 0.90 (0.77, 1.06)                 |
|                 | Arm B          | 7.4                      | 0.82 (0.70, 0.96) ORR                | 0.79 (0.67, 0.93)                 |

*Abbreviations: CI = confidence interval; HR = hazard ratio; ORR = overall response rate; OR = odds ratio; OS = overall survival; PS = performance status; RRS = rate of radical surgeries; OxCap = oxaliplatin/capecitabine; OxFU = oxaliplatin/leucovorin (LV)/infusional 5-FU.*

Figure 2  OS comparing OxCap and OxFU (unadjusted HR).

Figure 3  PFS in Arms A and B comparing OxCap and OxFU (unadjusted HR).

Toxicity and renal impairment  In the OxCap group, patients with CrCl 50–80 ml min⁻¹ had higher rates of G3 + nausea (Table 4), diarrhea and thrombocytopenia compared with patients of CrCl > 80 ml min⁻¹: 11%, 19% and 4% compared with 5%, 11% and 1%, respectively. There was also a higher rate of dose delays: 49% compared with 38%, respectively. In the OxFU group, there was no statistically significant difference for any of the toxicities or in dose modification between the two CrCl groups.

In the OxCap + cetuximab group, patients with CrCl 50–80 ml min⁻¹ had a higher rate of G3 + lethargy (29% vs 17%) and more reductions in the capecitabine dose (67% vs 53%) compared with those of CrCl > 80 ml min⁻¹.

In the OxFU + cetuximab group, G3 + neutropenia was higher in patients with CrCl 50–80 ml min⁻¹ compared with those of CrCl > 80 ml min⁻¹ (36% vs 23%) and so were the rates of dose delays (76% vs 66%) and reductions for both oxaliplatin (39% vs 26%) and 5-FU (56% vs 39%).

There was no difference in treatment-related deaths in any of the comparisons.

DISCUSSION

This paper compared OxCap with OxFU given in the XELOX and OXMDG regimens, respectively. The latter regimen is widely used in the United Kingdom and is similar to FOLFOX6 (Braun et al, 2003). XELOX and FOLFOX6 were compared in the French study reported by Ducruetz et al (2011), which showed in a per protocol analysis that XELOX is non-inferior to FOLFOX6 in terms of ORR (primary outcome measure), PFS and OS. Our retrospective analysis of the COIN data confirms that OxCap (XELOX) is equivalent to OxFU (OXMDG) in terms of the three efficacy measures, and is overall in line with the results of the meta-analysis by Arkenau et al (2008). However, the meta-analysis demonstrated an inferior ORR for OxCap (OR 0.85; 95% CI 0.74–0.97). Both ORR and RRS in our study were numerically
higher for OxFU; this reached statistical significance for RRs but not ORR despite the size of the study.

OxFU + cetuximab and OxFU + cetuximab were also equivalent in terms of OS, ORR and RRs. Nonetheless, PFS was longer for OxFU + cetuximab and this remained the case after repeating the analyses using only patients who were randomised before the protocol mandated capcitabine dose reduction. This observation is consistent with the positive interaction for cetuximab with the Fp partner in favour of S-FU, which was demonstrated by the exploratory analyses of Arm B vs Arm A (Maughan et al, 2011). A possible explanation would be the higher toxicity for OxFU + cetuximab, which led to more dose reductions and a lower total cumulative dose of oxaliplatin for patients on OxFU compared with OxFU in Arm A: 848 and 797 mg, respectively. This may be explained by the 6% higher cumulative dose of oxaliplatin for patients on OxFU compared with those of CrCl 80 ml min

The rate of patients who came off their second regimen after switching from OxFU (± cetuximab) to OxFU (± cetuximab) or vice versa was only 16%. This success in switching from one regimen to the other in keeping patients on first-line chemotherapy can be explained by the differing acceptability to patients of specific toxicity profiles.

Patients with CrCl 50–80 ml min

In conclusion: (I) OxFU (OxMDG) and OxFU (XELOX) have similar efficacy in the first-line treatment for aCRC. (II) OxFU is a better chemotherapy partner for cetuximab than OxFU because of less diarrhea and longer PFS. (III) Toxicity patterns differ and
thus the risks and preferences for the individual patient should inform the choice between OxCap and OxFU regimens. (IV) Switching to a different oxaliplatin/Fp regimen is a valid option in the event of controlled disease but poor tolerance or compliance and should be considered before abandoning this regimen and moving to a second-line regimen. (V) Patients with mild renal impairment on OxCap or OxFU + cetuximab should be monitored closely for the development of severe toxicities and early and appropriate dose reduction should be instituted if they occur.

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Conflict of interest

The authors declare no conflict of interest.

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