Capecitabine/oxaliplatin as first-line treatment for metastatic colorectal cancer: a meta-analysis
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CRD summary
This well-conducted review found that capecitabine and oxaliplatin treatment was equivalent to fluorouracil and oxaliplatin regimens for first-line treatment of metastatic colorectal cancer. However, the authors’ conclusions should be interpreted with some caution because the poor quality of the included studies makes the reliability of the results unclear.

Authors’ objectives
To determine the comparative efficacy and safety of capecitabine plus oxaliplatin (CAPOX) and fluorouracil plus oxaliplatin (FUOX) in first-line treatment of metastatic colorectal cancer.

Searching
Cochrane Colorectal Cancer Group Controlled Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, ISI databases and Chinese Biomedical Literature Database were searched between January 1998 and October 2008 without restrictions for relevant studies; search terms were reported. Proceedings from American Society of Clinical Oncology (ASCO), the American Association for Cancer Research and Gastrointestinal Cancers Symposium of ASCO were searched for additional studies. Reference lists of reviews and retrieved articles were checked for other studies.

Study selection
Randomised controlled trials (RCTs) in patients with metastatic colorectal cancer in which CAPOX was compared to FUOX administered with or without leucovorin as first-line treatment were eligible for inclusion. The primary outcome was progression-free survival. Secondary outcomes were overall survival, tumour response rate and the effects of treatment.

The included studies were conducted between 2006 and 2008. In the CAPOX intervention, capecitabine was given as 1,000 to 1,100mg/m² and oxaliplatin was given as 70 to 135mg/m² twice daily from days one to 11 to 14 every three weeks. The FUOX comparator comprised oxaliplatin given at 50 to 135mg/m² and fluorouracil given at doses that ranged from 250 to 2,250mg/m² (400mg/m² of fluorouracil was the most commonly reported dose). FUOX treatment was typically given once per week every two to six weeks. Leucovorin was given with the FUOX intervention in most trials and was administered at doses that ranged from 250 to 500mg/m².

Two reviewers independently performed the study selection; any disagreements were resolved by mutual discussions.

Assessment of study quality
Methodological quality was assessed by two reviewers independently using methods recommended by the Cochrane Collaboration for randomisation, allocation concealment, blinding and losses to follow-up. Any disagreements were resolved by discussion.

Data extraction
Data were extracted independently by two reviewers and used to calculate risk ratios (RR) and 95% confidence intervals (CI) for the outcomes. Any disagreements were resolved by discussion.

Methods of synthesis
Pooled risk ratios and 95% CIs were calculated using the Mantel-Haenszel fixed-effect model and DerSimonian and Laird random-effects model. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$. Results of the random-effects model were reported where there was significant statistical heterogeneity. The reviewers evaluated publication bias by visual appraisal of funnel plots. Sensitivity analyses were performed based on whether patients received leucovorin.
Results of the review
Ten RCTs (3,208 participants) were included in the review. Sample sizes in the trials ranged from 52 to 1,335 patients. Adequate randomisation was reported in seven studies. Allocation concealment and blinding were inadequate in three trials and were not clearly reported in seven trials. Losses to follow-up were stated for three studies. There were no statistically significant differences observed between CAPOX and FUOX treatments in tumour response rate, progression-free survival and overall survival. There was no significant statistical heterogeneity reported for any of these outcomes.

Treatment with CAPOX was associated with a statistically significant increase in symptoms of thrombocytopenia (RR 1.89, 95% CI 1.33 to 2.69, I²=0%) and hand-foot syndrome (RR 3.40, 95% CI 2.25 to 5.15, I²=0%). FUOX treatment was associated with a higher frequency of both neutropenia (RR 0.29 95% CI 0.15 to 0.55, I²=79%) and leucopenia (RR 0.41, 95% CI 0.18 to 0.95, I²=0%).

Sensitivity analyses where trials without leucovorin were omitted did not change the reported findings except for an advantage with FUOX treatment for diarrhoea (RR 1.47, 95% CI 1.22 to 1.78) with heterogeneity (I²=66%).

Authors' conclusions
Capecitabine and oxaliplatin treatment was equivalent to fluorouracil and oxaliplatin regimens for the first-line treatment of metastatic colorectal cancer.

CRD commentary
The review addressed a clearly defined question. Criteria for inclusion of studies in the review were stipulated. Appropriate electronic databases were searched without restriction and attempts were made to identify unpublished studies. Steps were taken throughout the review process to minimise errors and bias. The authors stated that they evaluated potential for publication bias, but they did not report the results of this analysis. The included trials were of poor quality, with no methods of allocation concealment or blinding reported for any trial. Most trials did not state losses to follow-up and it was not clear whether intention-to-treat analyses were performed in the trials. The authors acknowledged some of the limitations of the review pertaining to the variations in dose regimens, heterogeneity observed in of some of the outcomes pertaining to adverse events and insufficient data on some outcomes.

The review was well conducted. However, the results should be interpreted with some caution because of the poor quality of the included trials, especially the lack of information provided on losses to follow-up in most of the trials.

Implications of the review for practice and research
Practice: The authors stated that they would recommend use of capecitabine in combination with oxaliplatin as acceptable first-line treatment in patients with metastatic colorectal cancer.

Research: The authors did not state any implications for research.

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