Efficacy of oxaliplatin plus capecitabine or infusional fluorouracil/leucovorin in patients with metastatic colorectal cancer: a pooled analysis of randomized trials


CRD summary
The authors concluded that capecitabine plus oxaliplatin regimens reduced response rates compared to infusional fluorouracil plus oxaliplatin in metastatic colorectal cancer, and that treatments had similar effects on progression-free and overall survival. The authors' conclusions appeared to reflect the evidence, but the lack of reporting of review methods and trial quality make it difficult to be confident of their reliability.

Authors' objectives
To compare capecitabine plus oxaliplatin with infusional fluorouracil plus oxaliplatin for the treatment of patients with metastatic colorectal cancer.

Searching
MEDLINE, Cancer Lit, EMBASE, ISI Web of Science and Current Contents databases were searched from inception to January 2008. Search terms were reported. Trial registries, conference proceedings and reference lists of reviews and included studies were also searched. In addition, original trialists were contacted for details of any unpublished studies.

Study selection
Randomised controlled trials (RCTs) that compared capecitabine plus oxaliplatin with infusional fluorouracil plus oxaliplatin, in patients receiving first-line treatment for metastatic colorectal cancer, were eligible for inclusion. Trials had to report adequate statistical data. Trials that evaluated bolus fluorouracil plus oxaliplatin regimens were excluded. Two trials that used bevacizumab as part of the treatment regimen were included.

Review outcomes were response rate, progression-free survival, overall survival and relevant grade 3/4 toxicities.

The included trials evaluated different infusional fluorouracil and capecitabine-based regimens. Fluorouracil plus oxaliplatin regimens included bolus or infusional fluorouracil, leucovorin plus oxaliplatin. Trials were conducted in the USA or Europe.

The authors did not state how papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Summary statistical data for survival end points were obtained from published reports, plots, abstracts, slide presentations and personal communication. Hazard ratios and confidence intervals were preferred for time-to-event data (progression-free and overall survival), with log-rank p values or event counts if hazard ratios were not available. Odds ratios were calculated for binary data (toxicity and response rate).

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled odds ratios or hazard ratios and 95% confidence intervals were calculated primarily using a fixed-effect model; data were also analysed using random-effects models. Heterogeneity was assessed using the I^2 and χ^2 statistics. The response rate analysis was repeated excluding bevacizumab-containing regimens. Publication bias was assessed using a funnel plot.
Results of the review

Six randomised controlled trials (RCTs) were included (n=3,494 patients). Sample sizes ranged from 97 to 2,034 patients.

Response rates: Response rates ranged from 41 to 52% for infusional fluorouracil plus oxaliplatin regimens, and from 27 to 48% for capecitabine plus oxaliplatin regimens. Fluorouracil plus oxaliplatin regimens were associated with a statistically significant increase in the response rate compared to capecitabine plus oxaliplatin regimens, with an odds ratio of 0.85 (95% confidence interval (CI): 0.74 to 0.97; n=3,379 patients). No significant heterogeneity was found. Results were similar when bevacizumab-containing regimens were excluded.

Survival: There was no statistically significant difference between fluorouracil plus oxaliplatin and capecitabine plus oxaliplatin regimens for progression-free survival or overall survival. No significant heterogeneity was found. Results were similar when bevacizumab-containing regimens were excluded.

Toxicity (data only available from non-bevacizumab containing regimens): Fluorouracil plus oxaliplatin regimens were associated with a statistically significant reduction in grade 3/4 thrombocytopenia, odds ratio 2.07 (95% CI: 1.42 to 3.03; n=2,628 patients) and grade 2/3 hand-foot syndrome, odds ratio 3.54 (95% CI: 2.07 to 6.05; n=2,613 patients). Capecitabine plus oxaliplatin regimens were associated with a statistically significant reduction in neutropenia, odds ratio 0.15 (95% CI: 0.11 to 0.19; n=2,545 patients). There was significant heterogeneity for the analysis of diarrhoea (p=0.009) and neutropenia (p<0.00001). There were no significant differences between regimens for diarrhoea or for neuropathy.

Funnel plots showed no evidence of publication bias.

Authors' conclusions

Capecitabine plus oxaliplatin regimens reduced response rates compared to infusional fluorouracil plus oxaliplatin regimens in patients with metastatic colorectal cancer. The treatments had similar effects on progression-free and overall survival. Thrombocytopenia and hand-foot syndrome were more common with capecitabine-based regimens.

CRD commentary

The review question was clearly stated and inclusion criteria were defined. Several relevant sources were searched. Some attempts were made to minimise publication bias; funnel plots showed no evidence of publication bias. It was not clear if any attempts were made to minimise language bias. Methods used to select trials and extract data were not described, so it is not known whether efforts were made to reduce reviewer errors and bias. Only RCTs were included but trial validity was not assessed, so results from these trials and any synthesis may not be reliable.

Appropriate methods were used for the meta-analyses. Heterogeneity was assessed. However, treatment regimens varied and, as no data were presented on patient characteristics, there was possibly clinical heterogeneity among trials; in these cases re-analysing data using a random-effects model may have been appropriate. Many analyses that showed that significant effects had wide confidence intervals, which suggested the potential for underpowered analyses. Several authors disclosed that they acted as consultants or advisers for various pharmaceutical companies.

The authors’ conclusions appeared to reflect the presented evidence, but the lack of reporting of review methods and trial quality make it difficult to be confident of their reliability.

Implications of the review for practice and research

Practice: The authors stated that capecitabine plus oxaliplatin was a valid alternative for treating patients with metastatic colorectal cancer.

Research: The authors stated that capecitabine plus oxaliplatin could be viewed as appropriate standard treatment in future clinical trials.

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