A meta-analysis of chemotherapy regimen fluorouracil/leucovorin/oxaliplatin compared with fluorouracil/leucovorin in treating advanced colorectal cancer

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CRD summary
The review found significantly improved response rate and progression-free survival with fluorouracil/leucovorin/oxaliplatin compared with fluorouracil/leucovorin chemotherapy in advanced colorectal cancer treatment, but the incidence of grade 3 or 4 toxicities was significantly higher in the fluorouracil/leucovorin/oxaliplatin group. Given potential limitations in the review process and the uncertain quality of included trials, the authors’ conclusions should be treated with caution.

Authors’ objectives
To compare the efficacy and safety of fluorouracil/leucovorin/oxaliplatin and fluorouracil/leucovorin chemotherapy regimes in the treatment of advanced colorectal cancer.

Searching
MEDLINE and the Cochrane Library were searched from 1966 to November 2008 for publications in any language; search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared the efficacy and safety of fluorouracil/leucovorin/oxaliplatin and fluorouracil/leucovorin for the treatment of advanced colorectal cancer were eligible for inclusion. The criteria for patient eligibility included: colorectal adenocarcinoma with at least one bidimensionally measurable lesion according to World Health Organization (WHO) criteria; unresectable metastasis; normal bone marrow, hepatic, renal and cardiac function; WHO performance status 2 or more, or Karnofsky score of 50% or more; at least 18 years old; no previous chemotherapy or none within the previous six months. Trials were excluded if patients had: central nervous system metastasis; second malignancy; or a tumour in the former radiotherapy field. Trials using additional chemotherapeutic agents were also excluded.

Relevant outcomes were defined using WHO criteria. The primary outcome for efficacy was response rate (the sum of complete and partial responses). Other efficacy outcomes included: progression-free survival and overall survival (the secondary outcome). Relevant toxicity outcomes of Grade 3 or 4 were neutropenia, thrombocytopenia, anaemia, nausea, vomiting, diarrhea and neurological toxicity.

In included trials, the dosages used in the interventions were: infusion and or bolus of 400 to 2,600mg/m² 5-fluorouracil; infusion or bolus of 200 or 300mg/m² leucovorin; with the addition of an infusion of 85 or 125mg/m² oxaliplatin in the comparative group. Dosages were repeated every two, three or four weeks. One study used chronomodulated drug infusions. The mean age of included patients ranged from 59 to 63.5 years (median age ranged from 20 to 88 years, where reported (some trials excluded patients older than 76 years); the proportion of men ranged from 36 to 66.2%. Tumour location in the colon ranged from 64 to 77.0%; most of the remaining patients had tumours located in the rectum (range 15 to 34.0%); some patient tumours were multiple or not specified (range 0 to 15%). One included trial was of previously untreated patients, one was of second-line treatment and one was of third-line treatment.

Two independent reviewers performed the selection with disagreements resolved by consensus or using a third reviewer.

Assessment of study quality
The authors did not state that they assessed validity, but some study design details were reported.

Data extraction
Response rates (%) were extracted to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Median progression-free survival and overall survival (months) were also extracted, along with toxicity-related dose modification and discontinuation.

Two independent reviewers performed the extraction with disagreements resolved by consensus or using a third reviewer.

Methods of synthesis
Outcome data were pooled using weighted odds ratios with 95% confidence intervals, using a fixed-effects model (Peto) if significant heterogeneity was not present; a random-effects model (DerSimonian and Laird) was used if there was significant heterogeneity (p<0.05). Statistical heterogeneity was determined using the I² test. Sensitivity analyses were performed to detect potential heterogeneity.

Results of the review
Five RCTs were included in the review (n=1,421 patients, range 200 to 420). Three trials had a high percentage of crossover rates (range 57 to 71.3% from the fluorouracil/leucovorin group to the fluorouracil/LV plus oxaliplatin or irinotecan). One trial reported a high level of salvage surgery in both the fluorouracil/leucovorin (21%) and fluorouracil/leucovorin/oxaliplatin groups (32%). Two trials were multi-centred.

Efficacy: Fluorouracil/leucovorin/oxaliplatin was significantly more effective than fluorouracil/leucovorin chemotherapy for response rate (OR 4.02, 95% CI 2.37 to 6.82; I²=64.7%; five RCTs) and progression-free survival (OR not reported; five RCTs), but not significant for overall survival (four RCTs).

Toxicity: The incidence of grade 3 or 4 toxicities was significantly higher in the fluorouracil/leucovorin/oxaliplatin group than the fluorouracil/leucovorin group for neutropenia (OR 21.69, 95% CI 4.82 to 97.50; I²=48.9%; five RCTs), thrombocytopenia (OR 3.97, 95% CI 1.32 to 11.93; I²=23.5%; five RCTs), vomiting (OR 2.24, 95% CI 1.27 to 3.95; I²=1.7%; four RCTs), and neurological toxicity (OR 37.84, 95% CI 9.37 to 152.86; I²=0%; four RCTs), but not significant for anaemia (I²=0%; three RCTs), nausea (I²=49%; four RCTs), or diarrhoea (I²=89.5%; five RCTs). Toxicity related dose modification (OR 6.22, 95% CI 3.44 to 11.25; I²=37.8%; two RCTs) and toxicity related discontinuation (OR 3.13, 95% CI 1.36 to 7.19; I²=55.1%; four RCTs) were significantly higher in the fluorouracil/leucovorin/oxaliplatin group compared with the fluorouracil/leucovorin group.

Sensitivity analyses: Exclusion of two trials where chemotherapy was given as a second-line or third-line treatment did not significantly change the odds ratio for the response rate. For toxicity, the exclusion of two trials where treatment was over five days, significantly altered one result, giving a significantly higher diarrhoea rate in the fluorouracil/leucovorin/oxaliplatin group compared with the fluorouracil/leucovorin group (OR 2.96, 95% CI 1.77 to 4.97; I²=0%; three RCTs).

Authors' conclusions
Fluorouracil/leucovorin/oxaliplatin chemotherapy had better efficacy (response rate and progression-free survival) than fluorouracil/leucovorin in the treatment of advanced colorectal cancer. The incidence of grade 3 or 4 toxicities (neutropenia, thrombocytopenia, vomiting, and neurological toxicity) was significantly higher in the fluorouracil/leucovorin/oxaliplatin group than in the fluorouracil/leucovorin group, but these were manageable or reversible.

CRD commentary
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched in any language, but it appeared that unpublished studies were not considered. Publication bias was not assessed. Efforts were made to reduce error and bias in study selection and data extraction.

A formal validity assessment was not performed and little relevant information was provided to allow assessment of trial quality. Relevant study details were reported, but no details of length of follow-up or loss to follow-up were given.
There was methodological heterogeneity, which the authors acknowledged and stated may undermine their conclusions. There was also clinical heterogeneity, so pooling trial results may not have been appropriate. Statistical heterogeneity was assessed and there was evidence for heterogeneity with some outcomes. There were some discrepancies between $I^2$ values given in the text and those in the tables; this may be explained by the values in the text being for fixed-effects models and those in the tables for random-effects models. Confidence intervals were wide for some outcomes.

Analyses of progression-free survival and overall survival were unclear; quantitative data were not presented in the review. As such, it was unclear whether appropriate methods were used to calculate the time-to-event data. Sensitivity analyses were performed.

In view of some potential limitations arising from the review process and uncertainties about the quality of included trials, the authors' conclusions should be treated with caution.

**Implications of the review for practice and research**

**Practice:** The authors stated that for treatment with fluorouracil/leucovorin plus oxaliplatin, close attention should be paid to neutropenia and neurological toxicity (including acute cold-sensitive paraesthesia or cumulative peripheral neuropathy), which is dose-limiting and reversible.

**Research:** The authors identified a need for studies on how to prevent and treat neuropathy resulting from treatment with fluorouracil/leucovorin/oxaliplatin.

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