Irinotecan or oxaliplatin combined with 5-fluorouracil and leucovorin as first-line therapy for advanced colorectal cancer: a meta-analysis
Liang XB, Hou SH, Li YP, Wang LC, Zhang X, Yang J

CRD summary
This review concluded that oxaliplatin combined with 5-fluorouracil/leucovorin had a higher response rate and longer overall survival than irinotecan combined with 5-fluorouracil/leucovorin as first-line therapy for colorectal cancer. The reliability of the authors' conclusions is uncertain and they should be interpreted with caution given several weaknesses in the review including the poor quality of included trials and potential for bias.

Authors' objectives
To compare clinical efficacy and toxicity of irinotecan combined with 5-fluorouracil and leucovorin with those of oxaliplatin combined with 5-fluorouracil and leucovorin as first-line therapy for advanced colorectal cancer.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials Register (CENTRAL) and CBMdisc (Chinese Biology and Medicine disc) were searched for trials published in English before January 2010. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared irinotecan in combination with fluorouracil and leucovorin versus oxaliplatin combined with fluorouracil and leucovorin as first-line treatment for advanced or metastatic colorectal cancer were eligible for inclusion. Trials not analysed on intervention-to-treat basis were excluded.

Outcome measures were clinical efficacy (complete and partial response, stable and progressive disease, response rate, time to progression, duration of response, overall survival) and adverse effects (grade 3 or 4 toxicities according to the National Cancer Institute).

Included trials assessed irinotecan combined with fluorouracil and leucovorin, and combination regimen of oxaliplatin plus fluorouracil and leucovorin. Details of included patients (age, gender, proportion with Eastern Cooperative Oncology Group Performance Status (ECOG PS), adjuvant chemotherapy, liver or lung metastasis) were incompletely reported; however, the authors stated that these characteristics were similar across treatment groups.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Two reviewers independently assessed trial quality using Jadad scale. Key criteria assessed included: randomisation, double blinding, and withdrawals. Quality was rated on a scale of 1 (poorest) to 5 (best). In addition, adequacy of random allocation concealment was assessed, with results rated as A (adequate), B (unclear), C (inadequate), and D (not used). The authors did not report how any disagreements were resolved.

Data extraction
Two reviewers independently extracted data to calculate relative risks (RRs) and weighted mean differences (WMDs) with 95% confidence intervals (CIs). Where means and standard deviations were not reported, medians and ranges of outcomes were used. A standard format was used.

The authors did not report how any disagreements were resolved.

Methods of synthesis
Pooled relative risks and weighted mean differences, with corresponding 95% confidence intervals, were calculated using fixed-effect meta-analysis where there was no evidence for heterogeneity; otherwise random-effects meta-
analysis was used. Statistical heterogeneity was assessed using $X^2$ and $I^2$. Publication bias was assessed using a funnel plot.

**Results of the review**

Seven RCTs were included in the review (n=2,095 patients). All trials had a Jadad score of 2 (considered poor quality). Random allocation concealment was rated unclear in all trials.

**Clinical efficiency**

Oxaliplatin was associated with a significantly higher response rate (partial and complete) compared to irinotecan (RR 0.77, 95% CI 0.68 to 0.87; $I^2=23.6\%$; figures taken from the forest plot, which differed to those reported in the text; seven RCTs). Oxaliplatin was associated with a longer mean overall survival compared with irinotecan (WMD 2.04 months, 95% CI -3.54 to -0.54; n=1,875; six RCTs).

**Toxicity**

The incidence of grade 3/4 toxicity (nausea/emesis, diarrhoea, alopecia) was higher in the irinotecan group compared with the oxaliplatin group: nausea/emesis (RR 1.94, 95% CI 1.22 to 3.09; seven RCTs); diarrhoea (RR 1.71, 95% CI 1.34 to 2.18; seven RCTs); and alopecia (RR 14.56, 95% CI 4.11 to 51.66; n=791 patients; two RCTs). No differences between groups were found in the incidence of mucositis and febrile neutropenia.

However, the incidence of neurotoxicity (RR 0.06, 95% CI 0.03 to 0.14; n=2,095; seven RCTs), neutropenia (RR 0.70, 95% CI 0.55 to 0.91; seven RCTs) and thrombocytopenia (RR 0.18, 95% CI 0.05 to 0.61; n=1,151; four RCTs) were lower in the irinotecan group compared with the oxaliplatin group. No evidence of heterogeneity was found except for neutropenia.

There were no differences between groups in the incidence of dehydration, anaemia, or fatigue.

**Authors’ conclusions**

Oxaliplatin combined with 5-fluorouracil and leucovorin had a higher response rate and longer overall survival compared with irinotecan in combination with 5-fluorouracil and leucovorin. Irinotecan tended to result in more gastrointestinal tract reactions compared with oxaliplatin, but oxaliplatin was associated with neurotoxicity and myelosuppression.

**CRD commentary**

The review question was clearly stated. Relevant databases were searched but for English-only publications, so some relevant papers may have been missed. No searches were conducted for unpublished studies and the findings from funnel plots were not reported, so potential publication bias could not be ruled-out. Data extraction and quality assessment were conducted in duplicate, which reduced potential error and bias, but it was unclear whether a similar process was used during study selection.

The quality of included trials was assessed using Jadad scale; the results reported the quality to be generally poor. Details of included trials were incompletely reported. The decision to combine mortality outcome using weighted mean difference appeared inappropriate. A small number of trials with small sample sizes were summarised.

The reliability of the authors’ conclusion is uncertain given a number of weaknesses in the review process (potential for language and publication biases, risk of error and bias in study selection, incomplete reporting of trial details, and poor quality of included trials), so they should be interpreted with caution.

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

The authors did not state any implications for practice or further research.

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