Chronomodulated chemotherapy versus conventional chemotherapy for advanced colorectal cancer: a meta-analysis of five randomized controlled trials
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CRD summary
The review found the chronomodulated chemotherapy was more effective than conventional chemotherapy in improving overall survival in patients with advanced colorectal cancer without substantially increasing side effects. The authors' conclusions reflected the evidence base, but in light of shortcomings in the reporting of the review and the quality of the included trials, the authors' conclusions should be interpreted with caution.

Authors' objectives
To compare the efficacy and safety of chronomodulated chemotherapy with conventional chemotherapy in patients with advanced colorectal cancer.

Searching
PubMed, EMBASE and the Cochrane Library were searched for relevant studies published up to January 2009; search terms were not reported. Reference lists of retrieved studies were also searched.

Study selection
Eligible studies were randomised controlled trials (RCTs) of patients with advanced colorectal cancer that compared the efficacy or toxicity of chronomodulated chemotherapy with conventional chemotherapy. Treatment groups could only differ in the timing (not content) of treatment.

Eligible outcomes were median overall survival (defined as time from randomisation to death from any cause), objective response rate (defined as the sum of partial and complete response rates) and adverse events (graded according to World Health Organisation criteria).

In the included trials, mean age of participants was around 60 years; their performance status ranged from 0 to 2 on World Health Organisation criteria. In most patients, the primary tumour site was the colon. A minority of patients had had previous adjuvant treatment or previous surgery for metastases. The interventions all included fluorouracil combined with either oxaliplatin or irinotecan. Three trials also included folinic acid and one trial included leucovorin. Conventional chemotherapy was administered according to conventional dosing schedules; chronomodulated chemotherapy was administered according to circadian rhythms of the patients, but no further details were provided.

Two reviewers selected titles and abstracts, but no details were given for the methods used to select full papers.

Assessment of study quality
Validity assessment of the included trials was undertaken using the 5-point Jadad scale.

The authors did not state how the validity assessment was undertaken or how many reviewers performed the assessment.

Data extraction
Data were extracted for intention-to-treat populations in order to calculate hazard ratios (HRs), risk ratios (RRs) or odds ratios (ORs). If summary estimates and variances were not reported in the included trials, methods were used to estimate these values (Mahesh 1998).

Two reviewers extracted data, with disagreements resolved by iteration, discussion and consensus.

Methods of synthesis
Trials were combined in meta-analyses. Pooled overall hazard ratios for overall survival, relative risks for response rate and odds ratios for adverse events, with 95% confidence intervals (CIs), were calculated using a fixed-effect model. Heterogeneity was assessed using the Q test. If heterogeneity was confirmed, a random-effects model was used.

Subgroup analysis and sensitivity analysis were also used to investigate heterogeneity by excluding trials which potentially biased results. Publication bias was assessed using the Begg and Egger tests.

**Results of the review**

Five RCTs were included in the review (n=958 patients; range 48 to 564). Three trials scored 2 points, one trial scored 3 points and one trial scored 1 point on the Jadad scale. Limitations in quality included lack of blinding and lack of allocation concealment. The follow up of the trials ranged from 12 to 46 months.

**Efficacy**: Median overall survival was significantly increased with chronomodulated chemotherapy compared to conventional chemotherapy (HR 0.82, 95% CI 0.69 to 0.97; four RCTs). There was no evidence of significant heterogeneity. There was no evidence of a statistical difference in objective response rate, using a random-effects model (RR 1.27, 95% CI 0.88 to 1.83; five RCTs), but there was significant heterogeneity among studies (p=0.017).

**Safety**: A higher incidence of grade 3/4 mucositis (OR 2.26, 95% CI 1.34 to 3.83; two RCTs), asthenia (OR 2.15, 95% CI 1.3 to 3.56; three RCTs) and a lower incidence of grade 3/4 neutropenia (OR 0.26, 95% CI 0.16 to 0.42; three RCTs) was associated with chronomodulated chemotherapy. There was no evidence of a significant difference in the incidence of grade 3/4 diarrhoea, vomiting and nausea and peripheral sensory neuropathy between groups. Evidence of significant heterogeneity for some of these adverse events led to the post hoc exclusion of some trials and recalculation of summary estimates.

There was no evidence of significant publication bias (Begg test: P=0.81; Egger test: P=0.43).

**Authors’ conclusions**

Chronomodulated chemotherapy significantly improved overall survival in patients with advanced colorectal cancer compared with conventional chemotherapy, with predictable and manageable side effects.

**CRD commentary**

The review included a clear research question and inclusion criteria were appropriate. Three electronic databases were searched and attempts were made to find other relevant studies by searching reference lists of retrieved studies. Search terms were not reported, so it was not possible to assess how comprehensive the search was. The authors did not report whether there was language restriction, so language bias could not be excluded. No explicit attempts were made to search for unpublished studies, but there was no evidence of publication bias from formal assessments. The authors did not fully report methods for study selection or validity assessment, so reviewer error and bias could not be excluded.

The authors noted that three of the included studies were led by clinicians at the same hospital and that this suggested these trials were not completely independent, but they appeared to be separate trials. The median Jadad score for the quality of included trials was 2 out of a maximum of 5, but minimal information was given about the shortcomings of the individual trials, which made it difficult to evaluate the strength of the trial evidence.

The synthesis of included trials by meta-analyses was appropriate, but numbers of cycles and doses varied contributing to heterogeneity in the analyses and details of timings were not reported, which made it difficult to compare interventions. Some estimates were not robust and heterogeneity was significant; exclusion of trials contributing to the heterogeneity and recalculation of estimates resulted in different findings. These exclusions were made post hoc, and the individual characteristics contributing to the heterogeneity not described.

The authors’ conclusions reflected the evidence base, but in light of the shortcomings with the way the review was reported and the quality of the included trials, the authors’ conclusions should be interpreted with caution.

**Implications of the review for practice and research**
Practice: The authors stated that chronomodulated chemotherapy should be integrated into the early stages of anticancer drug development. It may be a valuable addition to current chemotherapy regimens and, in addition, it can be administered through dedicated drug delivery systems without hospitalisation constraints.

Research: The authors stated that further high quality RCTs are required, in particular to assess the risks of side effects from the chemotherapy regimens.

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