Systematic review of benefits and risks of second-line irinotecan monotherapy for advanced colorectal cancer

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CRD summary
The review assessed the benefits and risks of second-line irinotecan monotherapy for advanced colorectal cancer and found that this treatment was beneficial. Major shortcomings in the review process and a lack of relative comparisons between irinotecan and other approaches mean the authors’ conclusions should be considered with caution.

Authors’ objectives
To assess the benefits and risks of second-line irinotecan monotherapy for advanced colorectal cancer.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1990 to April 2007 for studies published in English, Dutch, German and French; search terms were reported. Reference lists of retrieved studies were searched.

Study selection
Eligible studies were phase 2 or phase 3 clinical trials of patients with locally advanced or metastatic colorectal cancer that included second-line palliative chemotherapy with systemically administered irinotecan monotherapy. Eligible outcomes included tumour response rate, median time to progression, median overall survival rate, severe adverse events and quality of life.

Most participants in the included studies were men (range 51% to 76%). Median age, where reported, ranged from 53 to 67 years. Most patients had a World Health Organization performance status of 0 or 1. Disease was more often located in the colon than the rectum. Irinotecan regimens included 350mg/m$^2$ every three weeks, 125mg/m$^2$ weekly for four consecutive weeks followed by a two-week rest period and other variable regimens. Some regimens used escalating doses or adapted doses to patient characteristics. In phase III trials, irinotecan was compared with best supportive care, fluorouracil by continuous infusion or irinotecan with the addition of granulocyte colony stimulating factor; weekly irinotecan was compared with three-weekly irinotecan. In one trial, those who reached either an objective response or disease stabilisation on irinotecan after 24 weeks were randomised to either stop or continue irinotecan.

The authors did not state how many reviewers performed study selection.

Assessment of study quality
The authors did not state whether quality assessment of the included studies was undertaken.

Data extraction
Data on the tumour response rate, median time to progression, median overall survival rate, incidence of severe adverse events (grades 1 to 4 for alopecia and grades 3 to 4 for other events) and quality of life scores were extracted according to how they were reported in the individual studies. Tumour response rates from phase 2 studies were recalculated according to the intention-to-treat principle. Tumour response rate was defined as the disease control rate (overall response and stable disease).

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

Methods of synthesis
The studies were synthesised in narrative format. Results were reported separately according to whether they were phase 2 or phase 3 trials.
Results of the review
Thirty studies (n=2,902) were included in the review: 25 phase 2 studies with 32 samples (n=1,894 participants) and five phase 3 studies with six samples (n=1,008).

Phase 2 trials: Disease control rate ranged from 26% to 73% (32 samples). Twenty-three samples reported a rate of at least 50%. Median time to progression ranged from 2.7 to 6.0 months (25 samples). Median overall survival ranged from 6.6 to 16.1 months (30 samples). Severe adverse events included severe diarrhoea (range 5% to 39%; 27 samples), nausea (range 1% to 24%; 16 to 24 samples), vomiting (range 2% to 22%; 19 to 27 samples), anorexia (range zero to 12%; nine samples), constipation (range zero to 6%; eight samples), mucositis (range zero to 3%; 12 samples), severe asthenia (range zero to 31%; 18 samples) and alopecia (range 32% to 100%; 16 samples). Treatment-related mortality of 2% was reported in two samples; the other 13 samples reported no treatment-related mortality. Quality of life scores were related to tumour response.

Phase 3 trials: Disease control rate ranged from 42.4% to 54.9% (two samples). Median time to progression ranged from 3.0 to 4.3 months (three samples). Median overall survival rate was greater than nine months in all six samples. Severe adverse events included diarrhoea (range 15% to 36%; six samples), nausea (range 5% to 14%; four to six samples), vomiting (range 6% to 14%; four to six samples), severe asthenia (range 4% to 21%; six samples), alopecia (86%; one sample) and treatment-related mortality (range zero to 5%; five samples). There was no evidence of a difference in quality of life between irinotecan and 5-fluorouracil. Patients who had irinotecan had better quality of life scores than patients who had supportive care (no figures reported). Quality of life scores on the weekly schedule of irinotecan were similar to scores on the three-weekly schedule (no figures reported).

Authors’ conclusions
In general, second-line treatment with irinotecan was beneficial to the patient with colorectal cancer.

CRD commentary
The review addressed a clear research question. Inclusion criteria appeared mostly appropriate, although the inclusion of phase 2 trials meant that the effects of irinotecan were not directly compared with other prospective approaches or treatments. A range of relevant sources was used for identifying studies. Restrictions on language and publication status meant that language and publication biases could not be ruled out. Methods for study selection and data extraction were not reported, so reviewer error and bias cannot be excluded. No quality assessment of included studies was undertaken, which made it difficult to determine the reliability of the evidence presented. The synthesis of studies in narrative format was appropriate. Most studies had no control arm, so it was unclear how the effects found with irinotecan compared with other treatments and management approaches. Control groups in the phase 3 studies varied, which made it difficult to determine the relative benefits and harms of irinotecan versus other approaches.

Major shortcomings in the review process and a lack of relative comparisons between irinotecan and other approaches mean the authors’ conclusions should be considered with caution.

Implications of the review for practice and research
Practice: The authors stated that decision making on treatment may be influenced by medical factors and personal preferences.

Research: The authors stated that the findings of this review could be used to assist the design of future research on second-line schedules with new treatment agents.

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Bibliographic details
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.