The effectiveness of intravenous 5-fluorouracil-containing chemotherapy after curative resection for gastric carcinoma: a systematic review of published randomized controlled trials


CRD summary
The authors concluded that limited evidence from studies of limited methodological quality suggests that intravenous 5-fluorouracil-containing chemotherapy could improve survival after curative gastrectomy, but further research is required before this treatment can be recommended. Overall, this was a well-conducted review. The authors’ conclusion takes account of the limitations of the evidence and is likely to be reliable.

Authors' objectives
To compare intravenous 5-fluorouracil (5-FU)-containing chemotherapy after curative resection for gastric carcinoma with surgery alone.

Searching
The Cochrane Library (Issue 2, 2006), PubMed and CBM-disc were searched up to May 2006 for studies published in any language; the search terms were reported. Reference lists were also screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review. Where reported, the duration of follow-up ranged from 3 to 10 years.

Specific interventions included in the review
Studies that compared intravenous 5-FU-containing chemotherapy after curative gastrectomy with surgery alone were eligible for inclusion. Studies in which neoadjuvant chemotherapy, intraperitoneal hyperthermic perfusion, radiotherapy or chemoimmunotherapy were administered were excluded. Most of the included studies were set in Western countries; others were set in Eastern countries. Where reported, the treatment duration ranged from 6 months to 5 years. Details of the treatment regimens were reported.

Participants included in the review
Studies of patients with stage I to III gastric adenocarcinoma were eligible for inclusion. The diagnosis had to be verified by gastroscopy and biopsy; patients with other types of malignancy or stage IV gastric carcinoma were excluded.

Outcomes assessed in the review
Studies that reported survival rates or survival curves were eligible for inclusion. The review also assessed side-effects. The primary review outcome was overall survival rate. The secondary review outcomes included disease-free survival rate, severe toxicities and chemotherapy-related mortality.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies. Any disagreements were resolved through consensus or with the aid of a third reviewer.

Assessment of study quality
Two reviewers independently assessed validity using the Jadad scale (randomisation, blinding and handling of withdrawals), allocation concealment and intention-to-treat analysis. Any disagreements were resolved through consensus or with the aid of a third reviewer.

Data extraction
Two reviewers independently extracted the data. Any disagreements were resolved through consensus or with the aid of a third reviewer. For each study, numbers of patients with overall or disease-free survival were extracted or estimated from survival curves at 3, 5, 7 and 10 years. It was unclear how studies with multiple treatment arms were handled.

**Methods of synthesis**

How were the studies combined?
Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a fixed-effect method (Mantel-Haenszel) in the absence of significant heterogeneity, and random-effects models in its presence.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. Analyses were repeated after excluding studies with the following characteristics: Jadad score less than 3; inadequate allocation concealment or intention-to-treat analysis; survival rates reported by direct statistical method; cointervention with oral 5-FU analogues. Subgroup analyses were conducted according to treatment regimen and Western or Eastern setting. Other potential reasons for differences between the studies were discussed.

**Results of the review**

Twenty-two RCTs (n=4,501) were included.

Five studies scored 3 points on the Jadad scale; the other studies scored 1 or 2 points. Details of the criteria met in the individual studies were given.

Survival.

Compared with surgery alone, intravenous 5-FU-containing chemotherapy after curative gastrectomy was associated with borderline, but statistically significant, increases in 3-, 5- and 7-year survival: the ORs were 1.49 (random-effects) (95% CI: 1.21, 1.84, p=0.0002; 22 studies), 1.41 (random-effects) (95% CI: 1.15, 1.74, p=0.001; 20 studies) and 1.32 (fixed-effect) (95% CI: 1.08, 1.62, p=0.007; 7 studies), respectively. There was no significant difference between treatments in 10-year survival (fixed-effect OR 1.51, 95% CI: 0.96, 2.36, p=0.07), but this analysis was based on only 2 studies (n=365). Statistically significant heterogeneity was detected for the analyses at 3 and 5 years (p=0.0003 and p=0.002, respectively). There was no significant improvement in disease-free survival at any time point with 5-FU-containing chemotherapy regimens compared with surgery alone.

Toxicity (15 studies reported severe chemotherapy-related toxicity events).

Intravenous 5-FU-containing chemotherapy was associated with an overall mortality rate of 1.1% (18 out of 1,629). The most common severe toxicities were haematological (leukopenia 14.3%, thrombocytopenia 4.9% and anaemia 4.7%) and gastrointestinal (nausea/vomiting/anorexia 13.4% and diarrhoea 6.4%). Other severe cardiac, pulmonary, renal and cutaneous toxicities were rare.

The results of subgroup analyses were also reported.

**Cost information**

None of the included studies evaluated cost-effectiveness.

**Authors’ conclusions**

There was some evidence that intravenous 5-FU-containing chemotherapy could improve survival after curative gastrectomy, but the methodological limitations of the included studies mean that further research is required to confirm these results before 5-FU-based chemotherapy can be recommended.

**CRD commentary**

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to minimise language bias. The absence of attempts to minimise publication bias might have resulted in the omission of other relevant studies. Validity was
assessed using specified criteria and the results of this assessment reported. Methods were used to minimise reviewer error and bias in the study selection, validity assessment and data extraction processes. The finding of significant heterogeneity for some of the meta-analyses shows that results were not consistent across studies. However, potential reasons for heterogeneity were explored and discussed. Overall, this was a well-conducted review. The authors’ conclusion takes account of the limitations of the evidence and is likely to be reliable.

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

Practice: The authors stated that further research is required before 5-FU-containing regimens after curative gastrectomy can be recommended.

Research: The authors stated the need for large-scale clinical trials to evaluate 5-FU-containing regimens after curative gastric surgery. High-quality RCTs are also required to evaluated neoadjuvant chemotherapy and chemoimmunotherapy. Future studies should also assess cost-effectiveness.

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