Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data


CRD summary
This review assessed the efficacy of chemotherapy regimens in prolonging overall survival in advanced gastric cancer. The authors concluded that the best results were achieved with a three-drug regimen containing fluorouracil, an anthracycline and cisplatin. This was a well-conducted review and the conclusion is likely to be reliable.

Authors' objectives
To assess the efficacy and tolerability of chemotherapy in patients with advanced gastric cancer.

Searching
MEDLINE, EMBASE, Cancerlit and the Cochrane Controlled Trials Register were searched to February 2005 without any language restrictions; the search terms were reported. In addition, relevant conference proceedings were searched, experts and drug manufacturers were contacted and references were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review. Crossover trials were excluded.

Specific interventions included in the review
Studies that compared systemic intravenous chemotherapy with alternative chemotherapy or best supportive care were eligible for inclusion. The included studies compared combination chemotherapy with best supportive care, single-agent with two-agent chemotherapy combinations, the triple-agent fluorouracil/cisplatin/anthracycline combination with either fluorouracil/cisplatin or fluorouracil/anthracycline two-agent combinations, and irinotecan-containing versus non-irinotecan-containing combinations.

Participants included in the review
Studies of patients with histologically confirmed advanced, recurrent, or metastatised adenocarcinoma of the stomach or gastroesophageal junction were eligible for inclusion. Studies that also included patients with oesophageal or pancreatic cancer were included if sufficient information was available on the subgroup of gastric cancer patients.

Outcomes assessed in the review
The primary review outcome was overall survival. Treatment-related deaths and quality of life were also assessed in the review.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the studies for inclusion in the review, and any disagreements were resolved by consensus with a third reviewer.

Assessment of study quality
The studies were assessed for validity using a customised validity scale based on published scales (see Other Publications of Related Interest). The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted the data, and any disagreements were resolved by consensus with a third
reviewer. Data on the interventions and the primary outcome of overall survival were extracted and hazard ratios (HRs) were calculated.

**Methods of synthesis**

How were the studies combined?
The studies were combined in fixed-effect meta-analyses and pooled HRs with 95% confidence intervals (CIs) were calculated. The potential for publication bias was assessed using funnel plots.

How were differences between studies investigated?
The studies were grouped on the basis of the interventions compared and combined in separate meta-analyses. Statistical heterogeneity was assessed using the chi-squared test. Clinical differences between the studies were explored in the text. Subgroup analysis was used to examine the influence on the results of some quality criteria.

**Results of the review**

Twenty-seven RCTs (n=4,198) were included in the review.

Chemotherapy versus best supportive care (3 RCTs, n=184): overall survival was significantly longer in the chemotherapy groups (all used combination therapy) than in the best supportive care groups (HR 0.39, 95% CI: 0.28, 0.52).

Combination versus single-agent chemotherapy (11 RCTs, n=1,472): overall survival was significantly longer in the combination groups (most used fluorouracil plus an anthracycline) than in the single-agent (mainly fluorouracil) chemotherapy groups (HR 0.83, 95% CI: 0.74, 0.93).

Fluorouracil/cisplatin/anthracycline versus fluorouracil/cisplatin combinations (3 RCTs, n=501): overall survival was significantly longer in the groups treated with three-agent combination chemotherapy than in those treated with the two-agent combination (HR 0.77, 95% CI: 0.62, 0.91).

Fluorouracil/cisplatin/anthracycline versus fluorouracil/anthracycline combinations (7 RCTs, n=1,147): overall survival was significantly longer in the groups treated with three-agent combination chemotherapy than in those treated with the two-agent combination (HR 0.83, 95% CI: 0.76, 0.91).

Irinotecan-containing chemotherapy combinations versus non-irinotecan-containing combinations (3 RCTs, n=536): there was no significant difference between the groups in length of overall survival: the HR was 0.88 (95% CI: 0.73, 1.06) in favour of irinotecan-containing combinations.

**Authors' conclusions**
The best survival results were achieved with a three-drug regimen of chemotherapy, containing fluorouracil, an anthracycline and cisplatin.

**CRD commentary**
The review question and the inclusion criteria were clear and highly specific. The search was extensive and included appropriate attempts to locate unpublished studies. This, together with the lack of language restrictions, reduces the possibility that some relevant studies were not included in the review. The authors reported using appropriate methods to minimise bias and error in the selection of studies for the review and the extraction of data, although not in the assessment of study validity. The validity assessment was, nevertheless, based on appropriate criteria, and was subsequently used to inform the analysis of the data. The decision to employ meta-analysis appears appropriate, and the authors' conclusions reflect the results of the evidence synthesis. This was a generally well-conducted review and the conclusions are likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research should evaluate the balance between relief of tumour-associated symptoms and treatment-associated toxicity of novel therapy regimens from the patient's perspective.

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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.