Neoadjuvant chemotherapy for advanced gastric cancer: a meta-analysis

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CRD summary

The authors concluded that neoadjuvant chemotherapy could improve tumour stage and survival rates in patients with locally advanced stomach cancer and had a good safety profile. The review findings were based on data from trials of diverse design and cointerventions, so they should be interpreted with caution.

Authors' objectives

To evaluate the effects of neoadjuvant chemotherapy in patients with locally advanced gastric cancer.

Searching

MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1978 to April 2010. Some search terms were reported. The meetings of the American Society of Clinical Oncology were scanned. Studies published as abstracts were eligible provided they presented sufficient data.

Study selection

Controlled clinical trials that compared neoadjuvant chemotherapy with no treatment before surgery in patients with locally advanced pathologically diagnosed gastric adenocarcinoma were eligible for inclusion. Trials had to perform neoadjuvant chemotherapy with oral, intravenous, intraperitoneal or an intra-arterial infusion. Patients had to have no history of prior treatment, but a history of potentially curative surgery. Trials of preoperative radiotherapy, immunotherapy and postoperative therapy and trials in patients with metastatic gastric cancer at recruitment were excluded.

The primary review outcome was the odds ratio (OR) of overall survival rate. Secondary outcomes were tumour-free margins resection (R0) rates and tumour down-staging rates (percentage in stage pT0-2 after surgery). The review also assessed adverse events.

The included trials evaluated a variety of different neoadjuvant chemotherapy regimens composed of one or more drugs (details were reported); some studies did not specify drug regimens. In some of the treatment and control groups, patients received postoperative chemotherapy. Most trials were set in Asian counties; other trials were set in Western countries.

Two reviewers independently selected studies.

Assessment of study quality

Trial validity was assessed using the Jadad criteria (defined in the review as adequate methods of randomisation, allocation concealment, patient and observer blinding and losses to follow-up). Trials that scored 4 or more points (out of a maximum possible score of 7) were classified as high-quality.

The authors did not state how many reviewers assessed validity.

Data extraction

Two reviewers independently extracted continuous data as mean differences and 95% confidence intervals (CIs) and dichotomous data as odds ratios with 95% confidence intervals.

Methods of synthesis

Pooled odds ratios and weighted mean differences (WMDs), with 95% confidence intervals, were calculated. Heterogeneity was assessed using Q statisitic and I^2. Fixed-effect models were used in the absence of significant statistical heterogeneity; otherwise random-effects models were used. The number needed to treat (NNT) was calculated where appropriate. One trial, with non-comparative staging data at baseline, was excluded from the analysis

of tumour down-staging.

Sensitivity analysis was conducted by separately analysing high-quality trials. Subgroup analysis was used to examine the influence of different factors including tumour grade, chemotherapy regimen and race.

A funnel plot was used to explore the potential for publication bias.

Results of the review

Fourteen trials were included in the review (n=2,271 patients). Treatment group size ranged from 19 to 253 patients. In four trials, randomisation was 'well reported'. Four trials used envelopes for allocation concealment. One trial was double-blinded. All trials reported withdrawals and drop-outs. Six trials scored 4 points or more out of 7 on the Jadad scale and were classified as high-quality. The median duration of follow-up was 54 months (range 24 to 83 months, where reported).

Overall survival: Neoadjuvant chemotherapy was associated with a marginally significant improvement in overall survival rate (48.1%) compared with no treatment (46.9%) in trials with a median follow-up of over three years (OR 1.27 , 95% CI 1.04 to 1.55; NNT=84; 12 trials, n=1,868 patients).

Progression-free survival: Neoadjuvant chemotherapy was associated with a significantly higher rate of progression-free survival at three years compared with no treatment (41% versus 28%; OR 1.85, 95% CI 1.39 to 2.46; NNT=8; three trials).

Tumour-down staging rate: Neoadjuvant chemotherapy was associated with a significantly higher rate of tumour-down staging compared with no treatment (50% versus 38%; OR 1.71 , 95% CI 1.26 to 2.33; NNT=9; five trials, n=718 patients)

R0 resection rate: Neoadjuvant chemotherapy was associated with a significantly higher R0 resection rate (75% versus 67%; OR 1.51, 95% CI 1.19 to 1.91; eight trials).

No significant heterogeneity was found for any of the above analyses.

There was no significant difference between neoadjuvant chemotherapy and control groups for perioperative mortality (three trials).

Side effects in neoadjuvant chemotherapy groups included grade 3/4 gastrointestinal problems (9%; three trials) and leukopenia (18%; three trials).

A funnel plot based on survival showed no obvious evidence for publication bias.

Authors' conclusions

Neoadjuvant chemotherapy could improve tumour stage and survival rate in patients with locally advanced gastric cancer and had a good safety profile.

CRD commentary

The review question was clearly stated. Inclusion criteria were appropriately defined. Several relevant sources were searched. Attempts were made to minimise publication bias by including studies reported as abstracts, but it was not clear if any language restrictions were applied. Methods were used to minimise reviewer errors and bias in the selection of studies and extraction of data, but it was not clear whether similar steps were taken during the validity assessment.

The validity assessment was undertaken using a tool designed for randomised controlled trials, but this may not have been appropriate as most of the trials appeared not to be randomised. The design of trials was not clear either. Data from trials of diverse design were pooled; given that most trials were apparently not randomised and may have been subject to various sources of bias, the reliability of review findings was unclear. The influence of various factors on the results was explored including trial quality. In the discussion section, the authors stated that, based on a subgroup

analysis of five trials that did not use postoperative chemotherapy, 'no clear conclusions could be reached on the effect of neoadjuvant chemotherapy alone on the overall survival rate'. This is in contrast to their overall conclusions.

The review conclusions were based on data from trials of diverse design that compared preoperative neoadjuvant chemotherapy with and without post-operative chemotherapy with no preoperative chemotherapy and so should be interpreted with caution.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further well-designed, adequately powered trials are required to identify the optimal neoadjuvant chemotherapy regimen and to evaluate new regimes in patients with locally advanced gastric cancer.

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