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Review

An updated meta-analysis of adjuvant chemotherapy after curative resection for gastric cancer

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Abstract

Objectives: To investigate whether and how much gastric cancer patients after curative resection could benefit from chemotherapy.
Patients and methods: Meta-analysis was conducted with all the qualified clinical randomized trials which compared adjuvant chemotherapy with surgery alone. The database includes MEDLINE, EMBase and CBM disc, and the censor data were up to November 2007. Primary outcomes were relative risk (RR) on death and disease-free survival (DFS); secondary outcomes include RR of adverse reactions of the two arms. Sub-group analysis and sensitivity analysis were also performed. All the calculations and statistical tests were done with the RevMan 4.2.8 software.
Results: Finally, 23 trials which included 4919 patients (2441 in the adjuvant chemotherapy arm, 2478 in the observation arm) achieved all the criteria. Among them, 19 studies reported the survival rate at the end of follow-up, 60.6% alive among 2286 patients in the adjuvant chemotherapy arm, 53.4% alive among 2313 patients in the observation arm, with the RR on death of 0.85 (95%CI: 0.80–0.90). Eight studies reported the DFS, and the observation arm had a shorter DFS (RR: 0.88, 95%CI: 0.77–0.99). Grade 3/4 of myelosuppression and GI toxicity occurred more frequently in the treatment arm. Nine studies reported the recurrence rate and suggested that the treatment arm had a lower recurrence rate (RR: 0.78, 95%CI: 0.71∼0.86).
Conclusions: Statistically, adjuvant chemotherapy could improve the survival rate and disease-free survival rate in gastric cancer after curative resection and reduce the relapse rate. However, the clinical benefits of adjuvant chemotherapy still need to be improved. Additionally, post-operative chemotherapy could be tolerated.

Keywords: Gastric cancer; Adjuvant chemotherapy; Randomized controlled clinical trial; Meta-analysis

Introduction

Gastric cancer is a leading cause of illness and death from cancer worldwide, with nearly a million new cases diagnosed each year. It is the fourth most common cancer and the second leading cause of cancer death worldwide.[1] The incidence of gastric cancer is different throughout the world. High incidence areas of gastric adenocarcinoma include East Asia, such as China and Japan. Low incidence rates are found in North and East Africa, and North America. Surgery is still the first choice of therapy; however, two-thirds of the patients were first diagnosed at an advanced stage of gastric cancer,[2] and the 5-year-survival rate has been disappointing. Therefore, the achievement of an increase in the rate of cure would be an important goal. Many clinical trials have evaluated the role of adjuvant therapy and, in particular, whether chemotherapy after curative resection may improve survival compared to the surgery alone. The first meta-analysis on adjuvant chemotherapy after gastrorectomy was initially published in 1993 by Hermans[3] and did not indicate a survival benefit. After that, the second study reported by Earle in 1999[4] indicated a weak survival benefit in the chemotherapy group, but the decision of excluding Asian trials probably introduced a selection bias. The third

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meta-analysis by Mari[5] confirmed the role of chemotherapy, but was questionable. In this meta-analysis, there were two studies[6,7] carried out in England which pooled chemotherapy and immunochemotherapy together. Two other studies[8,9] included in this study of Mari either involved patients with residual cancer or included the intervention of radiotherapy. The fourth meta-analysis published by Panzini in 2002[10] proved a survival benefit. It was uncertain whether the participants in one American study[11] had curative resection, and the result of another Italian trial,[12] updated in 2001,[39] was not accepted in this meta-analysis.

All four meta-analyses only confirmed the survival benefit, lacking the consequence of disease-free survival (DFS) and recurrence rate. Recently, as the application of new drugs and some new randomized clinical trials have reported, the significance of chemotherapy in gastric cancer should be reassessed. We systematized the available information to perform an updated meta-analysis of all the randomized clinical trials on chemotherapy versus observation alone after curative resection of gastric cancer, to analyze and examine the survival benefits and the adverse reactions with chemotherapy.

Subjects and methods

Search strategy and eligible criteria

This is an updated meta-analysis of all the studies published which met the following criteria. We considered all the randomized controlled trials that compared adjuvant chemotherapy versus observation alone after curative resection of gastric cancer. We searched MEDLINE, EMBase and CBM disc up to November 2007. The search strategy terms used in the English database were ''adjuvant chemotherapy'' AND ''gastric cancer OR stomach cancer OR stomach neoplasm OR gastric carcinoma'' AND ''randomized clinical trial''. Blindness is not necessary. Meanwhile, all patients should have undergone a potentially curative surgery.

Patients in the intervention group must have received systemic chemotherapy. Systemic administration was defined as by oral or by intravenous routes, but not including intraperitoneal infusion or immunotherapy. Randomized controlled trials comparing different dosing schemes and schedules of the same agent or a combination of agents were accepted.

Randomized controlled trials with three or more arms were retained if at least two arms addressed an eligible comparison. In case of overlapped or duplicated reports, only the main report with the maximal information was retained. We only considered studies published in journals. Results published only in meeting abstracts without full journal peer-review were excluded. We accepted studies with the languages in English.

We excluded non-randomized trials and pseudo-randomized trials with alternative allocation of subjects. Related overviews were excluded. Studies such as those including patients with metastasis or residual disease after surgery and those with immunotherapy and/or radiotherapy combined with chemotherapy, were also excluded.

Data extraction

From each eligible trial, we made a record of the authors, publication year, country of the investigator, sample size (total, eligible, and per arm), intervention regimen, agents of chemotherapy, cycles of chemotherapy, follow-up period, curative effect including survival rate, disease-free survival and recurrence rate, and adverse events during treatment period. Sites of recurrence or metastasis were also extracted.

Two reviewers (TSL, YW) assessed each trial independently. The methodological quality of trials was evaluated according to the Cochrane reviewers' handbook 4.2.3 RCT criteria[13] which include secure method of randomization, allocation concealment, patient and observer blinding, losses to follow-up and intention-to-treat analysis. Based on these criteria, the studies were divided into three categories from A (high quality) to C (low quality).

Statistical analysis

Software RevMan 4.2.8 was employed for the meta-analysis. Relative risks (RR) were expressed for dichotomous data like overall survival rate, disease-free survival rate, and recurrence rate. Continuous data like side-effects were expressed with weighted mean differences (WMD). Both were reported using 95 percent confidence intervals (95%CI).

All meta-analyses appraised inter-study heterogeneity using the Chi-square based Q statistic for statistical significance[14] and the I^2 statistic for the amount of heterogeneity,[15] with $P < 0.10$ being statistically significant and $I^2 > 50\%$ showing large heterogeneity. If there was no heterogeneity, fixed effects model was used; otherwise, a random effect model based on the DerSimonian and Laird estimator was used.[16] Publishing bias was tested by using the funnel plot.

Sensitivity analysis was performed to investigate the possible influence of the study quality. We re-analyzed the main outcome after excluding the trials of quality levels B and C. Furthermore, we performed sub-group analysis to capture interested information with different characteristics, such as lymph nodes invasion, depth of lesion, races, regimens, length of cycles and follow-up period.

Results

Eligible trials

A total of 556 studies were retrieved electronically, but 523 of them were found to be unrelated after reading the