Meta-analysis: the efficacy and safety of monoclonal antibody targeted to epidermal growth factor receptor in the treatment of patients with metastatic colorectal cancer

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CRD summary
This review concluded that monoclonal antibodies targeted to epidermal growth factor receptor could be effective in increasing response rates over chemotherapy or best supportive care, and could be a key therapeutic agent in the treatment of metastatic colorectal cancer despite a moderate increase in the rate of grade 3 or 4 adverse events. This conclusion is probably reliable.

Authors' objectives
To assess the efficacy and safety of using an anti-epidermal growth factor receptor (EGFR) monoclonal antibody in addition to a chemotherapy regimen in the treatment of patients with metastatic colorectal cancer.

Searching
PubMed and EMBASE were searched. Search terms were reported, but search dates were not. References of identified studies and review articles were checked and authors of identified trials were queried for additional studies. Abstracts of major gastroenterological meetings were screened. Only studies published in full in English or Chinese were eligible for inclusion (unless a translation was available).

Study selection
Randomised controlled trials (RCTs) that compared best supportive care or chemotherapy alone to the same best supportive care or chemotherapy plus anti-EGFR monoclonal antibody in patients with advanced or metastatic colorectal cancer were eligible for inclusion. Immunohistochemical evidence of EGFR expression was not required. Trials were required to report response rates using the RECIST criteria. Incidence of grade 3 or 4 adverse events was assessed.

Included studies assessed cetuximab at a dose of 400mg/m$^2$ in week one of the first cycle of treatment followed by 250mg/m$^2$ weekly or panitumumab at 6mg/kg every two weeks. Most trials used a chemotherapeutic regimen in conjunction with the anti-EGFR and as a control regimen; a range of regimens was used (capecitabine and oxaliplatin with or without bevacizumab, irinotecan with or without bevacizumab, oxaliplatin with bevacizumab, and 5-fluorouracil, oxaliplatin and leucovorin). Full details were reported in the paper. Two trials used best supportive care. Most trials enrolled patients with metastatic cancer; two trials enrolled patients with advanced disease.

The authors did not state how papers were selected for the review.

Assessment of study quality
Two reviewers assessed validity of the studies using the Jadad scale of up to five points for the criteria of randomisation, blinding and treatment of withdrawals and dropouts. Studies that scored fewer than 3 were considered to be of low quality. Differences were resolved through discussion and consultation with a third reviewer.

Data extraction
Data were extracted by two reviewers to permit the calculation of odds ratios (OR) with 95% confidence intervals (CI) using intention-to-treat principles. Differences were resolved through discussion and consultation with a third reviewer.

Methods of synthesis
Pooled odds ratios with 95% CI were calculated using a fixed-effect model unless there was statistically significant heterogeneity, in which case a Mantel-Haenszel random-effects analysis was adopted. Statistical heterogeneity between the studies was assessed using the $X^2$ test with a significance level of 0.05. A priori subgroup analyses were specified to examine the impact of anti-EGFR monoclonal antibody preparations. A sensitivity analysis was performed. Publication bias was assessed through visual inspection of funnel plots.
Results of the review
Seven RCTs (n=4,186) were included in the review. All were considered to be of high quality: four scored 5 points on the Jadad scale, two scored 4 points and one scored 3.

The pooled response rate for patients treated with an anti-EGFR monoclonal antibody was statistically significantly higher at 25.4% compared to 17.6% for patients in the control groups (OR 3.36, 95% CI 1.42 to 7.95; six RCTs). Subgroup analysis revealed a statistically significant effect in trials of cetuximab (OR 3.76, 95% CI 1.5 to 9.43; four RCTs), but not in the two trials that used panitumumab. There was a statistically significantly higher incidence of grade 3 or 4 adverse events in the anti-EGFR groups (OR 2.23, 95% CI 1.74 to 2.86; seven RCTs).

Individual adverse events with statistically significant increases in the anti-EGFR groups included diarrhoea, hypomagnesaemia and skin toxicity. Sensitivity analyses that excluded a low-quality study or studies that used panitumumab did not significantly change the results of the analyses. There was no evidence of publication bias.

Authors’ conclusions
Monoclonal antibodies targeted to EGFR could be effective in increasing response rates and could be a key therapeutic agent in the treatment of metastatic colorectal cancer despite a moderate increase in the rate of grade 3 or 4 adverse events.

CRD commentary
The review question and inclusion criteria were clear. Two relevant databases and some other sources were searched. The restriction to published studies reported in English or Chinese may have led to the omission of some relevant studies and increased the possibility of publication and language biases. Publication bias was assessed, but the value of funnel plot analysis was limited by the small number of studies. The authors appeared to use methods designed to reduce reviewer bias and error during data extraction and validity assessment, but did not report doing so for study selection. A recognised scale of some relevant criteria was used in the validity assessment. The decision to use meta-analyses was reasonable. Some steps were taken to assess and explore heterogeneity, although reporting of this was somewhat limited. The authors’ conclusions are reflective of the results of the review and are probably reliable.

Implications of the review for practice and research
Practice: The authors stated that monoclonal antibodies targeted to EGFR could be a key therapeutic agent in the treatment of metastatic colorectal cancer.

Research: The authors stated that further research was required to assess the toxicity and risk attached to combination treatment with anti-EGFR monoclonal antibodies and various chemotherapeutic regimens.

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