Is there a palliative benefit of gemcitabine plus fluoropyrimidines in patients with refractory colorectal cancer? A review of the literature
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CRD summary
The authors concluded that fluoropyrimidine plus gemcitabine was clinically active in patients with refractory colorectal cancer and demonstrated prolonged time to progression and acceptable toxicity when bolus 5-FU was not used. The conclusion reflected the results of the review, but uncertain quality of the included studies plus potential for missed studies and bias made its reliability difficult to determine.

Authors' objectives
To assess the efficacy and safety of fluoropyrimidine plus gemcitabine (FG) in patients with advanced colorectal cancer.

Searching
PubMed and The Cochrane Library databases and Ovid search engine were searched for English-language studies; search dates ranged from 1950 to 2008. Searches of American Society of Clinical Oncology abstracts from 1998 to 2008 were undertaken. Search terms were reported.

Study selection
Studies were eligible if they reported tumour response and tolerability using the FG combination in colorectal cancer patients and were undertaken as phase I or II trials. Narrative or retrospective reviews, case-control reports and studies that described predictors of response or pharmacokinetics were excluded.

The intervention for phase I studies comprised a weekly maximum tolerated dose of gemcitabine between 900 to 1,000mg/m^2 with either bolus 5-FU 450mg/m^2 plus folinic acid 100mg/m^2 or capecitabine 1,660mg/m^2/day for three weeks with one week off. The intervention for phase II studies comprised a weekly, or bi-weekly, dose of gemcitabine between 750 and 1,250mg/m^2 with continuous infusion 5-FU 200mg/m^2 or bolus 5-FU 450mg/m^2 plus folinic acid 100mg/m^2 or capecitabine 2,500mg/m^2/day.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The overall response rate, time to tumour progression and median survival were extracted for each study. Data were extracted by one reviewer and independently verified by three other reviewers.

Methods of synthesis
The studies were combined in a narrative synthesis grouped by efficacy and safety.

Results of the review
A total of eight studies were included in the review (n=258, range 18 to 60): two phase I studies (n=42) and six phase II studies (n=216).

In studies that used FG as first-line therapy (two studies) overall response rate ranged from 30.0 to 38.3%, time to progression was more than 8.3 months and median survival was more than 18 months.

Where FG was used as third-line therapy (four studies) stable disease was reported by 31.0% to 70.5% of patients,
median time to progression ranged from one to four months and median overall survival from 8.9 to 11.3 months. The most commonly reported grade 3-4 toxicities were neutropenia, thrombocytopenia and mucositis; neutropenia rates were over 10% in studies using bolus 5-FU (four studies); neutropenia rates were 8% or less in studies that used capecitabine or continuous 5-FU infusion.

Authors' conclusions
Fluoropyrimidine plus gemcitabine was clinically active in patients with refractory colorectal cancer and demonstrated prolonged median time to progression and acceptable toxicity only when bolus 5-FU was not used.

CRD commentary
The review question was clear and was supported by specific inclusion criteria. The authors searched several relevant databases, but the decision to limit the review to published studies reported in English increased the chances of publication and language biases and omission of relevant studies. Efforts were made to minimise errors and bias in the data extraction of studies; it was unclear whether such safeguards were in place when initially selecting studies for the review. No assessment of study validity was reported, which made it difficult to assess the reliability of the included data; most studies contained fewer than 60 patients and were neither prospective nor randomised. The decision to adopt a narrative synthesis was probably correct in view of the clinical heterogeneity among the studies. The conclusions reflected the results of the review, but poor reporting of the review methodology, the lack of a validity assessment and potential for publication and language biases made it difficult to determine their reliability.

Implications of the review for practice and research
Practice: The authors stated that FG may be considered for patients with advanced colorectal cancer who were refractory to primary treatment without other options or who are not eligible for clinical studies.

Research: The authors stated that further investigations in chemotherapy-naive or 5-FU resistant patients with advanced colorectal cancer of combination FG with an infusional 5-Fu regimen or capecitabine were required.

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