Meta-analysis on inoperable pancreatic cancer: a comparison between gemcitabine-based combination therapy and gemcitabine alone

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CRD summary
This review concluded that, compared with gemcitabine monotherapy, gemcitabine-based combination therapy may improve survival in patients with advanced pancreatic cancer. The review was generally well conducted and the authors’ conclusions appear justified, however, the clinical significance of the findings is unclear.

Authors’ objectives
To evaluate the role of gemcitabine (GEM)-based combination therapy compared with GEM monotherapy in patients with advanced pancreatic cancer.

Searching
Trials in any language were identified through a computerised bibliographic search of MEDLINE (1966 to 2006), EMBASE (1966 to 2006), CBM-disc (1981 to 2006), ASCO’s database of abstracts (1995 to 2005) and EBM Reviews (Cochrane Database of Systematic Reviews, Issue 1, 2006; ACP Journal Club, 1991 to 2006, DARE, Issue 1, 2006; the Cochrane CENTRAL Register, Issue 1, 2006). The search terms were reported.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a follow-up rate of at least 95% were eligible for inclusion.

Specific interventions included in the review
Studies of GEM-based combination therapy versus GEM monotherapy were eligible for inclusion. The details of combination therapies were reported in the study. Cisplatin (DDP) was used in several studies.

Participants included in the review
Studies in patients with histologically or cytologically proven pancreatic cancer were eligible for inclusion. Patients were required to have a baseline Karnofsky performance status of at least 50% (or Eastern Cooperative Oncology Group performance status of less than 2) and adequate haematological, renal, cardiac and hepatic function. Patients with an estimated life expectancy of at least 12 weeks were required to have received no chemotherapy, radiotherapy or other anti-tumour therapy in the 6 months prior to entry into the study.

Outcomes assessed in the review
Studies that reported overall survival were eligible for inclusion. The primary outcome assessed in the review was survival at 6 months. Other outcomes included survival at 1 year, objective remission rate, clinical benefit rate, time to progress/progress-free survival and toxicity. Toxicity profiles were reported according to the World Health Organization’s criteria.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed abstracts for inclusion and all potentially eligible trials were retrieved in full text and reviewed in more detail. The inclusion of relevant studies was by consensus.

Assessment of study quality
The trials were assessed for randomisation, masking, drop-outs and withdrawals. These criteria were used to assign a Jadad score of between 0 and 5. The authors did not state how the validity assessment was performed.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on the numbers of events in each group were used to calculate the risk difference (RD) and its 95% confidence interval.
confidence interval (CI) for each study. The numbers of cases of grade 3-4 toxic effects in each group were also recorded.

**Methods of synthesis**

**How were the studies combined?**
The studies were pooled by meta-analysis using both fixed-effect and random-effects models. Publication bias was assessed visually using funnel plots.

**How were differences between studies investigated?**
A chi-squared test was used to investigate statistical heterogeneity. A fixed-effect meta-analysis was used where there was no evidence of statistical heterogeneity, while a random-effects model was used if statistically significant heterogeneity was observed. A subgroup analysis investigated the effects of different types of combination therapy on 6-month survival.

**Results of the review**

Twenty-two RCTS (n=5,473) were included in the review: 7 phase II trials and 15 phase III trials.

The methodological quality of the included studies was good: all studies were considered to have a Jadad score of 3 or higher.

GEM combination therapy significantly improved overall survival at 6 months (22 trials; RD 0.04, 95% CI: 0.01, 0.06, p=0.008) compared with GEM monotherapy. There was no evidence of statistically significant heterogeneity (p=0.19). At 1 year, GEM combination therapy continued to significantly improve survival (21 trials; RD 0.03, 95% CI: 0.01, 0.05, p=0.01) compared with GEM monotherapy.

GEM combination therapy showed a statistically significant improvement in both the objective remission rate (21 trials; RD 0.04, 95% CI: 0.01, 0.07, p=0.02), where statistical heterogeneity was significant (p<0.0001), and the clinical benefit rate (6 trials; RD 0.10, 95% CI: 0.02, 0.17, p=0.01), where statistical heterogeneity was of borderline significance.

GEM combination therapy significantly improved the time to progress/progress-free survival rate at 6 months (13 trials; RD 0.07, 95% CI: 0.04, 0.10, p<0.00001) compared with GEM monotherapy. Statistical heterogeneity was not evident (p=0.20).

Grade 3-4 toxicity was significantly higher in GEM combination patients for neutropenia (21 trials; RD 0.05, 95% CI: 0.01, 0.10, p=0.02), thrombocytopenia (21 trials; RD 0.05, 95% CI: 0.02, 0.08, p=0.002) and vomiting/nausea (21 trials; RD 0.03, 95% CI: 0.00, 0.05, p=0.02).

A post-hoc subgroup analysis that stratified trials by type of combination therapy revealed that only the GEM plus targeted drug (marimastat, tipifarnib or erlotinib) combination versus GEM monotherapy yielded a significantly improved survival rate at 6 months (3 trials; RD 0.06, 95% CI: 0.01, 0.11, p=0.02).

Funnel plots for overall survival at 6 months and 1 year did not suggest the presence of publication bias.

**Authors’ conclusions**

Specific GEM combinations produced significant survival advantages compared with GEM alone in patients with advanced pancreatic cancer.

**CRD commentary**

The review addressed a clear question in terms of inclusion criteria, study design and outcomes of interest. A number of relevant electronic databases were searched and the search terms were reported. There were limited efforts to identify unpublished trials and some trials were published as abstracts only. The risk of publication bias was assessed. Steps were taken to minimise bias and error when making decisions about study relevance, but the methods used to extract the data were not reported. Study quality was assessed using a standard scale.
Details of drug combinations and outcome data for the included trials were provided, but not information about the dose and duration of the therapies. The lack of details about the study participants prevents the reader from assessing the appropriateness of combining studies. The studies were combined by meta-analysis and differences between the studies were investigated using a subgroup analysis. Statistical heterogeneity was investigated and was not significant for most outcomes; significant heterogeneity for some outcomes suggests that the decision to pool some studies might not have been appropriate. The authors' conclusions about GEM combination therapy appear to be based on the meta-analysis and seem reliable based on the evidence presented. However, the clinical significance of the findings is uncertain given the small magnitude of the survival benefit, increased risk of adverse events and lack of efficacy for most combinations.

**Implications of the review for practice and research**

Practice: The authors stated that GEM plus oxaliplatin and GEM plus erlotinib should be considered in patients with good performance, but should be carefully considered in weaker patients.

Research: The authors stated that further research, using individual patient data, is needed to determine the efficacy of GEM combination therapies for advanced pancreatic cancer.

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