Meta-analysis of inoperable pancreatic cancer: gemcitabine combined with cisplatin versus gemcitabine alone

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CRD summary
This review compared the therapeutic effects of gemcitabine (GEM) monotherapy with GEM-cisplatin (DDP) combination chemotherapy in patients with advanced stage pancreatic cancer. The authors concluded that the GEM-DDP combination should not be recommended and that GEM monotherapy remains the standard treatment for such patients. However, given the poor quality of the data, the findings may not be reliable.

Authors' objectives
To compare the therapeutic effects of gemcitabine (GEM) monotherapy with GEM-cisplatin (DDP) combination chemotherapy in patients with advanced stage pancreatic cancer (APCa).

Searching
The following were searched from inception to March 2005: MEDLINE, EMBASE, CBM-disc, the American Society of Clinical Oncology's database of abstracts, EBM Reviews, the Cochrane CENTRAL Register (Issue 1, 2005), the Cochrane Database of Systematic Reviews (Issue 1, 2005) and DARE (Issue 1, 2005). The search terms were reported. No restrictions on the language of publication were made.

Study selection
Study designs of evaluations included in the review
Well-designed randomised controlled trials (RCTs) that followed up more than 95% of participants were included in the review. The authors did not state what constituted a 'well-designed' study. Eligible studies also had to match participant groups for factors such as age, stage and performance status.

Specific interventions included in the review
Studies comparing intravenous infusion of GEM-DDP combination chemotherapy against intravenous infusion of GEM monotherapy were included. Dosages were not reported.

Participants included in the review
Patients with APCa, as well as those with locally advanced metastatic disease, were included in the review. Eligible patients were required to have: histologically or cytologically ascertained disease; a baseline Karnofsky performance status of at least 50% (or ECOG performance status less than 2); a life expectancy of at least 12 weeks; no chemotherapy, radiation therapy or other anti-tumour therapy in the last 6 months; and adequate haematological, renal, cardiac and hepatic function. Further details of the participants included in the eligible studies were not reported.

Outcomes assessed in the review
The primary outcome was overall survival, which included the survival curve or the clear end point of survival. A secondary outcome was the clinical benefit response, as derived from measurements of three parameters (performance status and weight) in most patients with APCa. Other end points were overall objective remission rate and toxicity.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the abstracts of the primary studies. If one reviewer considered an abstract might be eligible, the complete article was retrieved and reviewed in detail by both reviewers. The authors did not state how any disagreements were resolved.

Assessment of study quality
The methodological quality of the included studies was assessed using the Jadad scale (randomisation, masking, drop-outs and withdrawals). The studies were awarded a score between 0 (poor quality) and 5 (good quality).

The authors did not state how many reviewers performed the quality assessment.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Missing data were requested from the original study authors. All variables were defined as dichotomous data (e.g. 6-month survival rate was defined as alive or dead at 6 months after randomisation). Overall survival at 6 months and 1 year, 6-month time to progression/time to treatment failure, and Grade 3-4 toxic effects were extracted. The resulting treatment effects were standardised to obtain an effect size by risk difference (RD), described as the risk in the GEM-DDP combination group minus the risk in the GEM alone group. The authors did not appear to have used an intention-to-treat analysis.

**Methods of synthesis**
How were the studies combined?
The effect sizes from the included studies were combined in a meta-analysis using a fixed-effect model.

How were differences between studies investigated?
A chi-squared test was used to assess levels of heterogeneity between the included studies.

**Results of the review**
Six RCTs (n=560) were included in the review. Two hundred and seventy-eight patients were randomised to the GEM-DDP combination and 282 to GEM alone.

All of the included studies scored 3 points on the Jadad quality scale and were considered by the authors to be of high quality. No significant heterogeneity was detected in any of the meta-analyses, except adverse events.

A marginally significant improvement of 6% in objective remission rate was observed for the GEM-DDP combination group (5 studies; RD 0.06, 95% confidence interval, CI: 0.000, 0.12). There was no significant improvement in clinical benefit response for the GEM-DDP combination group (3 studies).

There was no significant improvement in 6-month survival rate for the GEM-DDP combination group (5 studies; RD 0.05, 95% CI: -0.03, 0.13).

There was a marginal significant improvement of 9% in 6-month time to progression/time to treatment failure for the GEM-DDP combination group (5 studies; RD 0.09, 95% CI: 0.01, 0.17).

Grade 3-4 toxicity was higher in the GEM-DDP combination group for neutropenia (RD 0.06, 95% CI: -0.01, 0.12), thrombocytopenia (RD 0.08, 95% CI: -0.03, 0.18) and vomiting or nausea (RD 0.11, 95% CI: -0.01, 0.22), but none of these findings were statistically significant. However, significant heterogeneity was detected and the number of studies included was not reported.

**Authors' conclusions**
The GEM-DDP combination should not be recommended. GEM monotherapy remains the standard treatment for patients with APCa.

**CRD commentary**
This review was based on well-defined inclusion criteria and an extensive search of electronic databases. However, the
authors made no apparent attempt to specifically look for unpublished data and although they stated that publication bias is unlikely, as many of their studies showed a negative effect, this is still of concern. The reviewers took steps to reduce selection bias by using more than one reviewer to assess study eligibility, but it is unclear from their methods whether similar care was taken when assessing the quality of the studies and extracting the study data.

The data given in the tables would have benefited from further detail, particularly of dose schedules and regimens, so that the reader could better assess the clinical heterogeneity between the studies. Even so, the authors' analysis indicated that no statistical heterogeneity was present. In general, the analysis was appropriate, although the use of hazard ratios for the time to event (survival) data would have been better. However, these data are not always available. In addition, the authors pointed out in their discussion that the number of participants in their meta-analysis might not have been large enough to demonstrate any statistical advantage in terms of overall survival, adverse events and clinical benefit response, and that a large RCT is required. However, this same degree of caution was not reflected in their overall conclusions, and the reader should bear this in mind when interpreting the authors' findings.

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

**Practice:** The authors stated that the GEM-DDP combination should not be recommended and that GEM monotherapy remains the standard treatment for patients with APCa.

**Research:** The authors stated that a large prospective RCT should be carried out, in which the GEM-DDP combination is compared with GEM alone in the treatment of APCa. They also stated that new regimens and schedules of drugs should be explored in future studies.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on
the reliability of the review and the conclusions drawn.