Does gemcitabine-based combination therapy improve the prognosis of unresectable pancreatic cancer?
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CRD summary
The authors concluded that gemcitabine combination therapy, compared with gemcitabine alone, modestly improved survival, but increased the side-effects. Despite some issues with the review process, the evidence was substantial and the authors implications for practice reflect the insufficient effectiveness of the available treatments for unresectable pancreatic cancer.

Authors' objectives
To assess whether gemcitabine-based combination therapy was superior to gemcitabine alone, for locally advanced or metastatic pancreatic cancer.

Searching
PubMed, EMBASE, The Cochrane Library, and abstracts from the American Society of Clinical Oncology were searched up to November 2011. No language restrictions were applied; search terms were reported. Reference lists from reviews and original articles were manually searched.

Study selection
Eligible for inclusion were randomised controlled open or blind trials of patients with histologically confirmed, locally advanced, or metastatic pancreatic ductal cancer. Eligible trials had to compare the efficacy of a gemcitabine combination versus gemcitabine alone. Quasi-randomised trials, studies of resection to cure pancreatic cancer, and studies of patients with multiple cancers were excluded. The outcomes of interest were the objective response rates (complete or partial), one-year overall survival, median overall or progression-free survival, and side-effects.

The included trials recruited patients with pancreatic cancer that was not resectable, and with no previous history of chemotherapy. All trials recruited patients with a life expectancy of at least 12 weeks, a Karnofsky performance status of 50 or more (or World Health Organization performance status of zero to two), and adequate liver, renal, and blood function. Where reported, patient age ranged from 22 to 96 years, and the percentage of males ranged from 35 to 72.7. The percentage of patients with metastatic cancer ranged from 19 to 100. Sixteen different combination therapies were used, and these were categorised by type of combination agent; platinum, fluoropyrimidine, camptothecin, or targeted agents.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
Two reviewers independently assessed quality, using the Jadad scale, for randomisation, double blinding, and withdrawals and dropouts. The maximum score was 5. Any discrepancies were resolved through discussion with a third reviewer.

Data extraction
The response rates, one-year overall survival, and side-effects (vomiting, diarrhoea, neutropenia, anaemia, and thrombocytopenia) were extracted to calculate risk ratios and 95% confidence intervals. The median overall and progression-free survival were extracted. With the exception of toxicity data, which were extracted for the safety population, all other outcomes were extracted on an intention-to-treat basis.

Two reviewers independently extracted the data; discrepancies were resolved through discussion with a third reviewer.

Methods of synthesis
A fixed-effect model, or where there was evidence of statistical heterogeneity, a random-effects model, was used to combine the extracted risk ratios and 95% confidence intervals. Statistical heterogeneity was assessed using Cochran's
Q and I², with I² of greater than 50% indicating heterogeneity.

Subgroup analyses were carried out by type of combination agent. Median overall and progression-free survival were assessed using paired t-tests. Publication bias was assessed through visual inspection of funnel plots.

**Results of the review**

Twenty-six RCTs, with 8,808 patients (8,743 calculated from table; range 83 to 743). The text stated that most trials had a Jadad score of 3, with three trials scoring 4, indicating high quality. The table reported that 22 trials scored 4, and four scored 5. It was unclear which trials were open label.

**Response rate and survival:** Patients receiving gemcitabine alone had statistically significant lower objective response rates than those on combination therapy (RR 0.72, 95% CI 0.63 to 0.83; 26 RCTs; I²=7%). One-year overall survival was statistically significantly better in patients receiving gemcitabine combination therapy (RR 0.90, 95% CI 0.82 to 0.99; 18 RCTs; I²=0).

**Side effects:** Compared with gemcitabine alone, combination therapy significantly increased the incidence of vomiting (RR 0.75, 95% CI 0.62 to 0.89; 22 RCTs; I²=37%), diarrhoea (RR 0.66, 95% CI 0.49 to 0.89; 18 RCTs; I²=0), and thrombocytopenia (RR 0.76, 95% CI 0.60 to 0.97; 25 RCTs; I²=67%). There were no significant differences for neutropenia and anaemia.

Subgroup analyses indicated that the only significant difference between combination treatments was for vomiting. In the paired t-tests, only gemcitabine plus fluoropyrimidine statistically significantly increased the median overall survival (p=0.038) and median progression-free survival (p=0.045). The authors found no evidence of publication bias in the funnel plots.

**Authors' conclusions**

Gemcitabine combination therapy, compared with gemcitabine alone, modestly improved survival, but increased the side-effects.

**CRD commentary**

The review question and inclusion criteria were clearly stated. A number of appropriate sources were searched for relevant data, without language restrictions. The authors reported that there was no evidence of publication bias, but there were gaps on the funnel plots indicating possible missing data. The data were extracted and quality was assessed by two people, but it was unclear whether this was true for study selection. Reviewer error and bias cannot be ruled out.

The quality of the included trials was assessed, using appropriate criteria, and the trials were reported to be of high quality, despite some discrepancies in their scores. It was unclear how many trials were open label and whether this had any effect on the findings. Twenty-six trials, with a large number of patients, were included in the review. Some trial and patient details were reported, but no information on the treatment regimens was given. Appropriate methods appear to have been used to combine the trial data, and the authors acknowledged that there was evidence of statistical heterogeneity for some outcomes.

Despite some issues with the review process, the evidence was substantial and the authors’ implications for practice reflect the insufficient effectiveness of the available treatments for unresectable pancreatic cancer.

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

**Practice:** The authors stated that the available treatments for unresectable pancreatic cancer were not sufficiently effective.

**Research:** The authors stated that further research was needed to investigate the mechanisms involved in drug resistance, in pancreatic cancer, to develop novel therapies that overcome drug resistance.

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