Gemcitabine-based cytotoxic doublets chemotherapy for advanced pancreatic cancer: updated subgroup meta-analyses of overall survival
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CRD summary
These subgroup meta-analyses explored active gemcitabine combinations and concluded that there was a significant survival benefit with gemcitabine combined with either capecitabine or oxaliplatin, but patients with poor Karnofsky Performance Status had shorter survival with the combinations than with gemcitabine alone. The conclusions reflected the evidence presented, but the results of the small subgroup analyses are unlikely to be definitive.

Authors' objectives
To explore, through subgroup meta-analysis, the effectiveness of active regimens that include gemcitabine, in treating pancreatic cancer.

Searching
The reviewers updated their previous systematic review by searching for relevant studies published in MEDLINE, EMBASE, CBMdisc, or ASCO abstracts, from April 2006 to May 2009, or in ESMO abstracts in 2008 or ECCO abstracts in 2007. The search terms were reported and no language restrictions were applied.

Study selection
Eligible studies were randomised controlled trials (RCTs) of patients with a histological or cytological diagnosis of pancreatic cancer that was locally advanced or metastatic and not surgically curable. Patients had to have a baseline Karnofsky Performance Status (KPS) score of at least 50% and adequate haematological, renal, cardiac, and hepatic function. Where estimated, their life expectancy had to be at least 12 weeks and they should not have had prior chemotherapy, radiation therapy, or other anti-tumour therapy in the six months prior to study entry. Eligible trials compared gemcitabine-based cytotoxic doublet chemotherapy against gemcitabine alone, reported the primary outcome measure of overall survival, and had a follow-up rate of over 95%.

In the included trials, the drug used in combination with gemcitabine varied and included capecitabine, cisplatin, irinotecan, oxaliplatin, and 5-fluorouracil. Two reviewers assessed studies for inclusion.

Assessment of study quality
Trial quality was assessed using the Jadad scale. The number of reviewers who assessed quality was not clear.

Data extraction
The data were extracted to calculate risk ratios for six-month and one-year overall survival, with their 95% confidence intervals. The number of reviewers who extracted the data was not clear.

Methods of synthesis
For each combination therapy, risk ratios and 95% confidence intervals, for overall survival at six and 12 months, were pooled using either a fixed-effect or the DerSimonian and Laird random-effects model. The random-effects model was used if statistical heterogeneity was identified (p<0.10) by the Cochran Q test. Sensitivity analyses were performed to assess the impact of single trials on the pooled estimates. Publication bias was assessed using funnel plots and the Egger test.

Results of the review
Eighteen trials (n=4,237, range 42 to 556) were included in the review. One had a Jadad score of two, while all the others scored three out of five.

Overall: Using a fixed-effect model for both outcomes, the gemcitabine combinations had a lower risk of mortality (higher overall survival) than gemcitabine alone at six months (RR 0.91, 95% CI 0.85 to 0.97; 18 RCTs) and at 12
months (RR 0.96, 95% CI 0.93 to 0.99; 17 RCTs). There was significant heterogeneity in the six-month analysis.

**Subgroups**: Combination therapy was associated with a statistically significant improvement in six-month overall survival for gemcitabine with capecitabine (RR 0.85, 95% CI 0.73 to 0.99) and gemcitabine with oxaliplatin (RR 0.80, 95% CI 0.70 to 0.91), but not for gemcitabine with 5-fluorouracil, with irinotecan, and with cisplatin. At one year, it was associated with a marginal statistically significant improvement for gemcitabine with oxaliplatin (RR 0.93, 95% CI 0.87 to 1.00), but not for the other combinations. For the six-month analyses, heterogeneity was statistically significant for gemcitabine with 5-fluorouracil. For the one-year analyses, heterogeneity was statistically significant for gemcitabine with cisplatin.

**KPS score**: Four trials (n=1,325) subgrouped patients into those with good or poor performance status. Combination therapy versus monotherapy was associated with higher six-month and 12-month mortalities in the poor subgroup.

Sensitivity analyses found that no single trial unduly influenced the overall findings, while the funnel plots and the Egger test found no indication of publication bias.

**Authors’ conclusions**
The meta-analysis indicated a significant survival benefit with gemcitabine when combined with either capecitabine or oxaliplatin, but patients with a poor KPS score had shorter survival with combination therapy than with gemcitabine alone.

**CRD commentary**
This review addressed a clear question, using appropriate and clearly defined selection criteria. The search was broad, but the details of the included trials were limited. It was unclear whether methods were used to reduce error and bias in the quality assessment and data extraction. Most of the included trials were of moderate quality and might have been subject to various forms of bias. The synthesis appears to have been appropriate and the results were clearly presented.

The conclusions reflected the evidence presented. The subgroup analyses were based on fewer aggregate data and their conclusions might not be definitive.

**Implications of the review for practice and research**
**Practice**: The authors stated that gemcitabine-based cytotoxic doublet chemotherapy should be the first-line treatment for advanced pancreatic cancer.

**Research**: The authors stated that new drugs should be tested in prospective clinical trials and different treatment strategies for patients with good or poor performance status should be considered.

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