Gemcitabine in the chemoradiotherapy for locally advanced pancreatic cancer: a meta-analysis

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CRD summary
This review found that there were some benefits in survival with gemcitabine-based chemoradiotherapy compared with conventional 5-fluorouracil-based chemoradiotherapy in patients with locally advanced pancreatic cancer. Some caution is required when interpreting the results of the review because of the paucity of evidence and the potential for bias in the analysis.

Authors' objectives
To compare the effects of gemcitabine-based chemoradiotherapy with 5-fluorouracil-based chemoradiotherapy in the treatment patients with locally advanced pancreatic cancer.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to December 2010; search terms were reported. Bibliographies of the included peer-reviewed studies were also searched for additional studies. There were no language restrictions.

Study selection
Comparative studies that compared gemcitabine-based chemoradiotherapy with 5-fluorouracil-based chemoradiotherapy in treatment-naive patients with locally advanced pancreatic cancer were eligible for inclusion. Primary outcome of eligible studies had to be overall survival.

In included studies, gemcitabine doses ranged from 250 to 600mg/m²/week and 5-fluorouracil was administered at 200-1,000 mg/m²/week. One study administered maintenance gemcitabine of 1,000mg/m²/week to patients in both treatment arms. In one trial, cisplatin was also administered at 30mg/m²/day to patients treated with gemcitabine-based chemoradiotherapy. The included target volume of radiotherapy treatment was the primary tumour and regional lymph nodes, with total doses ranging from 30 to 61.2Gy (where reported). The techniques for radiotherapy administration were four-field conformal radiotherapy, three-dimensional conformal radiotherapy and external beam radiation according to computerised tomography or magnetic resonance imaging image-based three-dimensional planning.

Two reviewers independently performed the study selection; any disagreements were resolved by consensus.

Assessment of study quality
Two reviewers assessed the methodological quality of the included randomised controlled trials (RCTs) using the Jadad 5-point scale. Items assessed were randomisation, allocation concealment, blinding, and the adequate description of withdrawals and drop-outs. Trials that scored 2 points or below were assessed as low quality; trials with scores of 3 or more points were judged to be of high quality. Any disagreements between the reviewers were resolved by consensus.

Data extraction
Data were extracted to calculate risk ratios (RR) and 95% confidence intervals (CI) for survival at six months, 12 months, 24 months, and outcomes for toxicity of treatment. The authors did not explicitly state how many reviewers performed the data extraction.

Methods of synthesis
Pooled risk ratios and 95% confidence intervals were calculated. Heterogeneity was assessed using Cochran's X² and I².

Post-hoc sensitivity analyses were undertaken by excluding the retrospective study, excluding a small RCT, and excluding the RCT with an additional chemotherapeutic agent with gemcitabine.

The potential for publication bias was evaluated by visual appraisal of a funnel plot.
Results of the review
Four studies (229 patients) were included in the review including three RCTs and one retrospective study. Sample sizes ranged from 19 to 114 patients. The Jadad scores for the three RCTs were 3 points; the retrospective study was not assigned a score for methodological quality.

There were statistically significant benefits of gemcitabine-based chemoradiotherapy with higher survival rates at 12-months follow up (RR 1.54, 95% CI 1.05 to 2.26; \(I^2=0\%\)) compared with 5-fluorouracil-based chemoradiotherapy. There were no differences between the chemoradiotherapy regimens at six-months or 24 months of follow-up.

Sensitivity analyses showed a similar pattern of results at 12-months follow-up with higher survival rates observed with gemcitabine-based chemoradiotherapy compared with 5-fluorouracil-based chemoradiotherapy when the trial including an additional chemotherapeutic agent was excluded from the analysis (RR 1.51, 95% CI 1.00 to 2.29; \(I^2=0\%\); three studies, 167 patients) and when the smallest trial was excluded from the analysis (RR 1.59, 95% CI 1.06 to 2.37; \(I^2=0\%\); three studies, 210 patients).

In the sensitivity analysis of the three RCTs, there were no significant differences between the treatment groups at six-months or 12-months follow-up, but the survival rate at 24 months was higher for the gemcitabine-based chemoradiotherapy (RR 5.49, 95% CI 1.01 to 29.87, three RCTs; \(I^2=0\%\); 115 patients).

There were significantly more adverse events observed with gemcitabine-based chemoradiotherapy compared to 5-fluorouracil-based chemoradiotherapy with increased leucocytopenia (RR 5.02, 95% CI 1.86 to 13.54; three studies), thrombocytopenia (RR 6.10, 95% CI 1.69 to 21.99; three studies) and gastro-intestinal bleeding (RR 4.26, 95% CI 1.25 to 14.48). There were no significant differences between the treatment groups in anaemia.

The funnel plots for survival at six months, 12 months and 24 months showed some asymmetry, which suggested the possibility of publication bias.

Authors' conclusions
The results of the meta-analysis showed some benefits of gemcitabine-based chemoradiotherapy compared with 5-fluorouracil-based chemoradiotherapy in the treatment of locally advanced pancreatic cancer, particularly for survival at 12 months. The acute toxicity associated with gemcitabine-based treatment should be carefully considered.

CRD commentary
The review addressed a clear question. Some criteria for the inclusion of studies were outlined. Appropriate databases were searched with no language restrictions. There were no attempts to identify unpublished studies. The authors evaluated the potential for publication bias using appropriate methods; some publication bias was evident. Steps were taken to minimise errors and bias for the performance of study selection and quality assessment, but were not reported for data extraction.

The quality of the included RCTs was moderate. The results of the included studies were pooled in a meta-analysis, including the results from a retrospective non-randomised study. As the results from the non-randomised study would be associated with a number of potential biases, pooling the studies in this way may not have been appropriate. There was some methodological heterogeneity among the studies. Limited details were provided about the patients. The authors conducted sensitivity analyses to explore the effects of particular studies on the results. There were wide confidence intervals for some results. The authors acknowledged some of the limitations of the review such as the paucity of trials and the small numbers of patients in the included studies.

The review results should be interpreted with some caution because of paucity of evidence and the potential for bias in the analysis.

Implications of the review for practice and research
Practice: The authors stated that the acute toxicity associated with gemcitabine-based chemoradiotherapy should be carefully regarded when considering this treatment for patients with acute pancreatic cancer.

Research: The authors stated that further large RCTs were required on gemcitabine-based chemoradiotherapy in the treatment of locally advanced pancreatic cancer.
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