Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer

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CRD summary
This review concluded that significant survival benefits were observed for advanced pancreatic cancer patients when gemcitabine was combined with platinum analogues or fluoropyrimidines; good performance status patients also benefited from gemcitabine-based cytotoxic combinations. The conclusions reflected the results of the review and appear likely to be reliable, although the uncertain quality of the included trials should be borne in mind.

Authors' objectives
To assess the efficacy of gemcitabine-based combination chemotherapy for advanced and metastatic pancreatic cancer.

Searching
PubMed was searched to 2006; search terms were reported. The annual meetings of the American Society of Clinical Oncology and the European Cancer Conference were searched for additional studies.

Study selection
Randomised controlled trials (RCTs) of patients with histologically confirmed locally advanced or metastatic pancreatic cancer treated with first-line chemotherapy, using single-agent gemcitabine in the control arm and gemcitabine-based two-drug combination chemotherapy in the experimental arm, were eligible for inclusion. Studies conducted in adjuvant or neoadjuvant settings were excluded, as were trials investigating targeted agents such as metalloproteinase inhibitors, tipifarnib, erlotinib, bevacizumab or cetuximab. The primary outcome was overall survival; the reporting of adequate survival data was required for inclusion in the review.

In included trials, comparisons were: gemcitabine plus platinum analogue (oxaliplatin or cisplatin) versus single-agent gemcitabine; gemcitabine plus fluoropyrimidines (5-fluorouracil or capecitabine) versus single-agent gemcitabine; and gemcitabine plus other cytotoxic agents (irinotecan, exatecan or pemetrexed) versus single-agent gemcitabine. In most of the trials, gemcitabine was given at a dose of 1000mg/m² for seven out of eight weeks, followed by a weekly drug application for three out of four weeks. The proportion of males ranged from 46 to 66%. The proportion of patients with metastatic disease ranged from 54 to 100. The fraction of patients with a good performance status ranged from 24 to 88%.

Three reviewers independently selected studies for inclusion in the review.

Assessment of study quality
One reviewer assessed trial quality using the Jadad scale.

Data extraction
Two reviewers independently extracted overall survival data from which hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Additional data, where necessary, was derived from medical experts and the pharmaceutical industry.

Methods of synthesis
Trials were pooled using both fixed-effect and random-effects models. Heterogeneity was assessed using $X^2$ and $I^2$ statistics.

A priori subgroup analyses were conducted to examine differences by comparing good performance status (Karnofsky performance status - KFS - of 90 to 100%; Eastern Cooperative Oncology Group - ECOG - score of 0 to 1) and poor performance status cohorts (KPS of 60 to 80%; ECOG score of 2).
Publication bias was assessed using funnel plots.

Results of the review

Fifteen RCTs (n=4,465 patients, range 83 to 832) were included in the review.

Compared with gemcitabine alone, significant survival benefits were observed for any gemcitabine-based combination therapy (HR 0.91, 95% CI 0.85 to 0.97; I²=0%; 15 RCTs), fluoropyrimidine-based combinations (HR 0.90, 95% CI 0.81 to 0.99; I²=0%; six RCTs), and platinum-based combinations (HR 0.85, 95% CI 0.76 to 0.96; I²=0%; five RCTs).

No risk reduction was observed in the group of trials combining gemcitabine with irinotecan, exatecan or pemetrexed (four RCTs).

For patients with a good performance status, a significant benefit from combination chemotherapy was observed (HR 0.76, 95% CI 0.67 to 0.87; I²=0%, five RCTs), but patients with an initially poor performance status did not appear to benefit from combination chemotherapy (five RCTs).

Funnel plots suggested a low likelihood of publication bias.

Authors’ conclusions

A significant survival benefit was observed when gemcitabine was either combined with platinum analogues or fluoropyrimidines. Based on a preliminary subgroup analysis (representing 38% of all patients included in this meta-analysis), pancreatic cancer patients with a good performance status appeared to benefit from gemcitabine-based cytotoxic combinations, whereas patients with a poor performance status seemed to have no survival benefit from combination chemotherapy.

CRD commentary

The review question was clear and supported by appropriate inclusion criteria. A limited literature search was undertaken for suitable studies. It was unclear whether language restrictions were applied or unpublished studies were sought, so some studies may have been missed. The likelihood of publication bias was assessed and found to be low. Study selection and data extraction were performed in duplicate, to reduce the chance of error or bias, but study quality assessment was undertaken by one reviewer, so may have been subject to error and bias.

The authors stated that they used the Jadad scale to assess trial quality, but no details of this assessment were reported, which made it difficult to determine the reliability of the included trials. The decision to use meta-analyses was appropriate. Reasonable measures were used to assess and explore heterogeneity between trials.

The authors’ conclusions reflected the results of the review and appear likely to be reliable, although the uncertain quality of the included trials should be borne in mind.

Two authors disclosed financial links with Lilly Germany (gemcitabine drug manufacturers).

Implications of the review for practice and research

Practice: The authors stated that combination chemotherapy may help to improve treatment efficacy in patients with a good performance status, and that patients with a poor performance status should probably receive single-agent gemcitabine.

Research: The authors stated that future trials may consider separate treatment strategies for patients with good and poor performance status. The effects of intensive treatment on patients with good performance status should be evaluated and new treatments should be sought for patients with poor performance status.

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