Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer

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CRD summary
This well-conducted review reliably concluded that there is evidence to support the use of gemcitabine-based combination chemotherapy for the treatment of advanced pancreatic cancer.

Authors' objectives
To assess and compare the effectiveness of chemotherapy for locally advanced pancreatic cancer.

Searching
MEDLINE, OLDMEDLINE, CancerLit, EMBASE, and ISI Web of Science (including Science Citation Index, ISI Science and Technology Proceedings and Current Contents) were searched from inception; further details of the search were reported online. Conference proceedings and trial registries were also searched, as were reference of selected articles and previous systematic reviews. Original trialists were contacted for details of possible unpublished trials.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies evaluating chemotherapy treatments were eligible for inclusion. Specific comparisons included: chemotherapy versus best supportive care; fluorouracil (FU) versus FU-based combination chemotherapy; single-agent versus another single-agent chemotherapy; FU versus gemcitabine chemotherapy; gemcitabine alone versus gemcitabine-based combination chemotherapy regimens; gemcitabine versus novel agent; gemcitabine alone versus gemcitabine plus a novel agent; and regional versus systemic chemotherapy. Details of the various intervention and comparator regimens are available on the Journal of Clinical Oncology website (accessed March 2008; a subscription may be required for access).

Participants included in the review
Studies of patients with locally advanced/metastatic pancreatic adenocarcinoma were eligible for inclusion. Studies where patients were also treated for cancers other than exocrine pancreatic cancers and where data were not available for the relevant subset of patients were excluded from the review.

Outcomes assessed in the review
The primary outcome was overall survival, defined as time from random assignment to death; alternative definitions were also accepted. Studies which fulfilled the other inclusion criteria but did not report overall survival were included in the review, but not the meta-analyses.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the relevance of abstracts and any disagreements were resolved through discussion.

Assessment of study quality
Two reviewers independently assessed the quality of the studies according to method of random assignment, allocation concealment, blinding and losses to follow-up. Studies were graded as adequate, inadequate or unknown for each of the criteria.

Data extraction
Two reviewers independently extracted the data. Trial authors were contacted for additional data if required. Time-to-event data were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). If HRs were not available, where possible they were estimated from other relevant data including survival curves.
Methods of synthesis
How were the studies combined?
The studies were grouped and pooled HRs with 95% CIs were calculated using a fixed-effect model, or a random-effects model if there was evidence of significant statistical heterogeneity. Funnel plots were used to assess publication bias.

How were differences between studies investigated?
Forest plots were visually inspected for evidence of heterogeneity. Statistical heterogeneity was assessed using the chi-squared and I-squared statistics. The studies were grouped according to intervention type and subgroup analyses performed according to the following four categories: gemcitabine plus platinum agents, FU, irinotecan or capecitabine. Other potential sources of heterogeneity, such as differing outcome definitions, were also investigated.

Results of the review
Fifty-one RCTs (n=9,970) met the inclusion criteria, and of these 33 RCTs(n=6,026) provided sufficient data to be included in the meta-analyses.

Compared with best supportive care, chemotherapy significantly improved overall survival (HR 0.64, 95% CI: 0.42, 0.98; 6 RCTs), but there was evidence of significant heterogeneity. There were no significant differences in survival between FU-based combination therapy and FU-single agent chemotherapy (HR 0.94, 95% CI: 0.82, 1.08; 5 RCTs), or between gemcitabine and FU (HR 0.75, 95% CI: 0.42, 1.31; 2 RCTs), although there was significant evidence of heterogeneity for the latter result. Gemcitabine-based combination therapy had significantly improved survival in comparison with gemcitabine alone (HR 0.91, 95% CI: 0.85, 0.97; 14 RCTs).

Subgroup analyses suggested that platinum-based therapies (HR 0.85, 95% CI: 0.74, 0.96; 3 RCTs) and capecitabine (HR 0.83, 95% CI: 0.72, 0.96; 3 RCTs) in combination with gemcitabine reported significantly better survival than single-therapy gemcitabine. Irinotecan-based therapies (HR 1.01, 95% CI: 0.84, 1.22; 2 RCTs) and FU-based combination therapies were not significantly better than single-therapy gemcitabine.

There was evidence of publication bias for all comparisons.

Authors’ conclusions
Chemotherapy demonstrated a significant survival benefit over best supportive care, as did gemcitabine combination therapy over gemcitabine. This evidence supports the use of gemcitabine-based combination chemotherapy for the treatment of advanced pancreatic cancer.

CRD commentary
This well-conducted review answered a clear review question, using a thorough search for both published and unpublished studies. Some evidence of publication bias was suggested from funnel plots, but the authors were right to advise caution given the small number of studies included in many of the funnel plots. Attempts were made to reduce the risk of reviewer error and bias throughout all stages of the review process. The validity of the studies and level of heterogeneity were considered in the analyses, suggesting that the findings are reliable. Overall, the review conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further trials are required to delineate the best gemcitabine-based combinations, especially those involving capecitabine and platinum-based analogues. The authors also stated that there are a number of ongoing trials of interest and that an updated analysis would be required in order to incorporate these new data.

Funding
Cancer Research UK.
Bibliographic details

PubMedID
17577041

DOI
10.1200/JCO.2006.09.2551

Original Paper URL
http://jco.ascopubs.org

Indexing Status
Subject indexing assigned by NLM

MeSH
Antineoplastic Agents /therapeutic use; Antineoplastic Combined Chemotherapy Protocols /therapeutic use; Deoxycytidine /analogs & derivatives /therapeutic use; Fluorouracil /therapeutic use; Humans; Neoplasm Metastasis; Outcome Assessment (Health Care); Pancreatic Neoplasms /drug therapy /pathology; Randomized Controlled Trials as Topic

AccessionNumber
12007002800

Date bibliographic record published
07/02/2008

Date abstract record published
09/08/2008

Record Status
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.