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[Intervention Review]

Gemcitabine-based chemotherapy for advanced biliary tract carcinomas

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ABSTRACT

Background

Biliary tract cancers are a group of rare heterogeneous malignant tumours. They include intrahepatic and extrahepatic cholangiocarcinomas, gallbladder carcinomas, and ampullary carcinomas. Surgery remains the optimal modality of therapy leading to long-term survival for people diagnosed with resectable biliary tract carcinomas. Unfortunately, most people with biliary tract carcinomas are diagnosed with either unresectable locally-advanced or metastatic disease, and they are only suitable for palliative chemotherapy or supportive care.

Objectives

To assess the benefits and harms of intravenous administration of gemcitabine monotherapy or gemcitabine-based chemotherapy versus placebo, or no intervention, or other treatments (excluding gemcitabine) in adults with advanced biliary tract carcinomas.

Search methods

We performed electronic searches in the Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, MEDLINE, Embase, LILACS, Science Citation Index Expanded, and Conference Proceedings Citation Index – Science up to June 2017. We also checked reference lists of primary original studies and review articles manually, for further related articles (cross-references).

Selection criteria

Eligible studies include randomised clinical trials, irrespective of language or publication status, comparing intravenous administration of gemcitabine monotherapy or gemcitabine-based combination to placebo, to no intervention, or to treatments other than gemcitabine.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We assessed risks of bias of the included trials using definitions of predefined bias risk domains, and presented the review results incorporating the methodological quality of the trials using GRADE.

Main results

We included seven published randomised clinical trials with 600 participants. All included trials were at high risk of bias, and we rated the evidence as very low quality. Cointerventions were equally applied in three trials (gemcitabine plus S-1 (a combination of tegafur, gimeracil, and oteracil) versus S-1 monotherapy; gemcitabine plus S-1 versus gemcitabine monotherapy versus S-1 monotherapy; and gemcitabine plus vandetanib versus gemcitabine plus placebo versus vandetanib monotherapy), while four trials compared gemcitabine plus cisplatin versus S-1 plus cisplatin; gemcitabine plus mitomycin C versus capecitabine plus mitomycin C; gemcitabine plus oxaliplatin versus chemoradiotherapy; and gemcitabine plus oxaliplatin versus 5-fluorouracil plus folinic acid versus best supportive care. The seven

trials were conducted in India, Japan, France, China, Austria, South Korea, and Italy. The median age of the participants in the seven trials was between 50 and 60 years, and the male/female ratios were comparable in most of the trials. Based on these seven trials, we established eight comparisons. We could not perform all planned analyses in all comparisons because of insufficient data.

Gemcitabine versus vandetanib
One three-arm trial compared gemcitabine versus vandetanib versus both drugs in combination. It reported no data for mortality, health-related quality of life, or tumour progression outcomes. We rated the increased risk of serious adverse events, anaemia, and overall response rate as very low-certainty evidence.

Gemcitabine plus cisplatin versus S-1 plus cisplatin
From one trial of 96 participants, we found very low-certainty evidence that gemcitabine can lower the risk of mortality at one year when used with cisplatin versus S-1 plus cisplatin (risk ratio (RR) 0.76, 95% confidence interval (CI) 0.58 to 0.98; P = 0.04; participants = 96). The trial did not report data for serious adverse events, quality of life, or tumour response outcomes. There is very low-certainty evidence that gemcitabine plus cisplatin combination leads to a higher risk of high-grade thrombocytopenia compared with S-1 plus cisplatin combination (RR 5.28, 95% CI 1.23 to 22.55; P = 0.02; participants = 96).

Gemcitabine plus S-1 versus S-1
From two trials enrolling 151 participants, we found no difference between the two groups in terms of risk of mortality at one year or risk of serious adverse events. Gemcitabine plus S-1 combination was associated with a higher overall response rate compared with S-1 alone (RR 2.46, 95% CI 1.27 to 4.75; P = 0.007; participants = 140; trials = 2; I^2 = 0%; very low certainty of evidence). Neither of the trials reported data for health-related quality of life or time to progression of the tumour.

Gemcitabine plus oxaliplatin versus 5-fluorouracil plus folinic acid versus best supportive care
One three-arm trial compared gemcitabine plus oxaliplatin versus 5-fluorouracil plus folinic acid versus best supportive care. It reported no data for serious adverse events, health-related quality of life, or tumour progression. We rated the evidence for mortality and for overall response rate as of very low certainty.

Gemcitabine plus oxaliplatin versus 5-fluorouracil plus cisplatin plus radiotherapy
One trial of 34 participants compared gemcitabine plus oxaliplatin versus 5-fluorouracil plus cisplatin plus radiotherapy. It reported no data for quality of life, overall response rate, or tumour progression outcomes. We rated the evidence for mortality and serious adverse events as of very low certainty.

Gemcitabine plus mitomycin C versus capecitabine plus mitomycin C
One trial of 51 participants compared gemcitabine plus mitomycin C versus capecitabine plus mitomycin C. It reported no data for serious adverse events, quality of life, or tumour progression. We rated the evidence for mortality, overall response rate and thrombocytopenia as of very low certainty.

We also identified three ongoing trials evaluating outcomes of interest for our review, which we can incorporate in future updates.

For-profit bias: there was a high risk of for-profit bias in two trials (because of industry sponsorship) while there was a low risk of for-profit bias in another three trials, and unclear risk in two trials.

Authors' conclusions

In adults with advanced biliary tract carcinomas, the effects of gemcitabine or gemcitabine-based chemotherapy are uncertain on mortality and overall response compared with a range of inactive or active controls. The very low certainty of evidence is due to risk of bias, lack of information in the analyses and hence large imprecision, and possible publication bias. The confidence intervals do not rule out meaningful benefits or lack of effect of gemcitabine in all comparisons but one on mortality where gemcitabine plus cisplatin is compared with S-1 plus cisplatin. Gemcitabine-based regimens showed an increase in non-serious adverse events (particularly haematological toxicities). Further randomised clinical trials are mandatory, to further explore the best therapeutic options for adults with advanced biliary tract carcinomas.

PLAIN LANGUAGE SUMMARY

Gemcitabine-containing chemotherapy for people with advanced bile duct cancer

Review question

What are the benefits and harms of gemcitabine-based chemotherapy versus placebo or no intervention or gemcitabine-based chemotherapy versus chemotherapy without gemcitabine in people with advanced bile duct cancer?

Background
Bile duct cancer (starting in the bile duct) is an uncommon malignant tumour. In most people, bile duct cancer is diagnosed at an advanced stage. For them, treatment options include drugs (chemotherapy). Gemcitabine is a drug used to treat certain types of cancerous tumours, including advanced bile duct cancer. Gemcitabine is an active chemotherapy drug, and in combination with cisplatin has been the accepted standard treatment in this disease.

Study characteristics

The review authors searched published medical articles to clarify the role of gemcitabine (given by injection into a vein) compared with placebo (an inactive substance or preparation used as a control intervention in an experiment), or with no intervention, or with non-gemcitabine chemotherapy combinations in the treatment of people with advanced bile duct cancer. The review authors looked for randomised clinical trials, where people were allocated at random to one of two or more treatments groups, in order to perform statistical analysis from which to draw conclusions about the intervention. The evidence is current to June 2017.

Key results

The review authors found seven randomised clinical trials, and judged all of them to be at high risk of bias. These trials randomised 600 people with advanced bile duct cancer. The majority of these trials suggested that there were no demonstrable differences in either benefits or harms between gemcitabine-containing chemotherapy regimens compared with non-gemcitabine chemotherapy combinations. Only one trial, comparing gemcitabine plus cisplatin versus S-1 plus cisplatin suggested that gemcitabine-containing regimens might decrease death. The review authors identified three ongoing randomised clinical trials.

As far as funding goes, two of the seven trials were sponsored by the pharmaceutical industry, three were not sponsored by the industry, and the remaining two trials provided no information about funding.

Quality of the evidence and conclusions

The evidence obtained from the seven low-quality randomised trials was insufficient to prove whether or not gemcitabine-containing combinations are better than non-gemcitabine-containing combinations for people with advanced bile duct cancer. Moreover, gemcitabine-based combinations showed an increase in non-serious adverse events, particularly haematological toxicities (damage to blood and body tissues). More randomised clinical trials are needed.