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Gemcitabine-based chemotherapy for advanced biliary tract carcinomas (Review)

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[Intervention Review]

Gemcitabine-based chemotherapy for advanced biliary tract carcinomas

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A B S T R A C T

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.

P L A I N   L A N G U A G E   S U M M A R Y

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.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.   Gemcitabine plus vandetanib compared with vandetanib for advanced biliary tract carcinomas

Gemcitabine plus vandetanib compared with vandetanib for advanced biliary tract carcinomas

Patient or population: people with advanced biliary tract carcinomas
Setting: specialist hospitals
Intervention: gemcitabine plus vandetanib
Comparison: vandetanib

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with vandetanib	**Risk with gemcitabine plus vandetanib**				
All-cause mortality at 1 year	Not reported					
Serious adverse events	Study population		RR 0.95 (0.52 to 1.74)	117 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	271 per 1000	258 per 1000 (141 to 472)				
Health-related quality of life	Not reported					
Overall response rate	Study population		RR 5.40 (1.25 to 23.29)	113 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	36 per 1000	193 per 1000 (45 to 832)				
Time to progression of the tumour	Not reported					
Grade 1 - 4 anaemia	Study population		RR 7.12 (0.90 to 56.08)	117 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	17 per 1000	121 per 1000 (15 to 951)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RCT:** randomised clinical trial

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

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[1]Downgraded three levels (-3) because of i) within-study risk of bias due to high risk of bias; ii) publication bias could not be assessed; iii) imprecision due to small number of trials (one trial)

Summary of findings 2.   Gemcitabine versus vandetanib for advanced biliary tract carcinomas

Gemcitabine compared with vandetanib for advanced biliary tract carcinomas

Patient or population: people with advanced biliary tract carcinomas
Setting: specialist hospitals

Intervention: gemcitabine

Comparison: vandetanib

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Risk with vandetanib	Risk with gemcitabine				
All-cause mortality at 1 year	Not reported					
Serious adverse events	271 per 1000	214 per 1000 (111 to 412)	RR 0.79 (0.41 to 1.52)	115 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
Helath-related quality of life	Not reported					
Overall response rate	36 per 1000	135 per 1000 (29 to 619)	RR 3.77 (0.82 to 17.33)	108 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
Time to progression of the tumour	Not reported					
Grade 1 - 4 anaemia	17 per 1000	125 per 1000 (16 to 984)	RR 7.38 (0.94 to 58.05)	115 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RCT:** randomised clinical trial

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1]Downgraded three levels (-3) because of i) within-study risk of bias due to high risk of bias; ii) publication bias could not be assessed; iii) imprecision due to small number of trials (one trial)

Summary of findings 3.   Gemcitabine plus cisplatin compared with S-1 plus cisplatin for advanced biliary tract carcinomas

Gemcitabine plus cisplatin compared with S-1 plus cisplatin for advanced biliary tract carcinomas

Patient or population: people with advanced biliary tract carcinomas
Setting: specialist hospitals
Intervention: gemcitabine plus cisplatin
Comparison: S-1 plus cisplatin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with S-1 plus cisplatin	**Risk with gemcitabine plus cisplatin**				
All-cause mortality at 1 year	Study population		RR 0.76 (0.58 to 0.98)	96 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	809 per 1000	614 per 1000 (469 to 792)				
Serious adverse events	Not reported					
Health-related quality of life	Not reported					
Overall response rate	Study population		RR 0.82 (0.37 to 1.82)	88 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	238 per 1000	195 per 1000 (88 to 433)				

Time to progression of the tumour	Not reported				
Grade 1 - 4 anaemia	Study population		RR 11.27 (4.41 to 28.83)	96 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]
	85 per 1000	959 per 1000 (375 to 1000)			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RCT:** randomised clinical trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
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Summary of findings 4.   Gemcitabine plus S-1 compared with S-1 for advanced biliary tract carcinomas

Gemcitabine plus S-1 compared with S-1 for advanced biliary tract carcinomas

Patient or population: people with advanced biliary tract carcinomas
Setting: specialist hospitals
Intervention: gemcitabine plus S-1
Comparison: S-1

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with S-1	**Risk with gemcitabine plus S-1**				
All-cause mortality at 1 year	Study population		RR 0.61 (0.33 to 1.13)	151 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[1]	
	707 per 1000	431 per 1000 (233 to 799)				
Serious adverse events	Study population		RR 1.05 (0.15 to 7.10)	90 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	

	43 per 1000	46 per 1000 (7 to 309)				
Health-related quality of life	Not reported					
Overall response rate	Study population		RR 2.46 (1.27 to 4.75)	140 (2 RCTs)	⊕⊝⊝⊝ VERY LOW[1]	Not supported by Trial Sequential Analysis
	141 per 1000	346 per 1000 (179 to 669)				
Time to progression of the tumour	Not reported					
Grade 1 - 4 anaemia	Study population		RR 1.26 (1.00 to 1.59)	151 (2 RCTs)	⊕⊝⊝⊝ VERY LOW[1]	
	480 per 1000	605 per 1000 (480 to 763)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio; __RCT:__ randomised clinical trial

__GRADE Working Group grades of evidence__
__High certainty:__ We are very confident that the true effect lies close to that of the estimate of the effect.
__Moderate certainty:__ We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
__Low certainty:__ Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
__Very low certainty:__ We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded three levels (-3) because of i) within-study risk of bias due to high risk of bias; ii) publication bias could not be assessed; iii) imprecision due to small number of trials (two trials)

Summary of findings 5. Gemcitabine plus oxaliplatin compared with best supportive care for advanced biliary tract carcinomas

Gemcitabine plus oxaliplatin compared with best supportive care for advanced biliary tract carcinomas

__Patient or population:__ people with advanced biliary tract carcinomas
__Setting:__ specialist hospitals
__Intervention:__ gemcitabine plus oxaliplatin
__Comparison:__ best supportive care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with best supportive care	Risk with gemcitabine plus oxaliplatin				
All-cause mortality at 1 year	Study population		RR 0.78 (0.53 to 1.15)	40 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	889 per 1000	693 per 1000 (471 to 1000)				
Serious adverse events	Not reported					
Health-related quality of life	Not reported					
Overall response rate	Study population		RR 34.00 (2.11 to 547.54)	40 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	0 per 1000	0 per 1000 (0 to 0)				
Time to progression of the tumour	Not reported					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio; __RCT:__ randomised clinical trial

__GRADE Working Group grades of evidence__
__High certainty:__ We are very confident that the true effect lies close to that of the estimate of the effect.
__Moderate certainty:__ We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
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[1]Downgraded three levels (-3) because of i) within-study risk of bias due to high risk of bias; ii) publication bias could not be assessed; iii) imprecision due to small number of trials (one trial)

Summary of findings 6.   Gemcitabine plus oxaliplatin compared with 5-fluorouracil plus folinic acid for advanced biliary tract carcinomas

__Gemcitabine plus oxaliplatin compared with fluorouracil plus folinic acid for advanced biliary tract carcinomas__

__Patient or population:__ people with advanced biliary tract carcinomas

Setting: specialist hospitals
Intervention: gemcitabine plus oxaliplatin
Comparison: fluorouracil plus folinic acid

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with fluorouracil plus folinic acid	**Risk with gemcitabine plus oxaliplatin**				
All-cause mortality at 1 year	Study population		RR 0.81 (0.55 to 1.20)	41 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	857 per 1000	694 per 1000 (471 to 1000)				
Serious adverse events	Not reported					
Helath-related quality of life	Not reported					
Overall response rate	Study population		RR 2.15 (0.64 to 7.29)	41 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	143 per 1000	307 per 1000 (91 to 1000)				
Time to progression of the tumour	Not reported					

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RCT:** randomised clinical trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded three levels (-3) because of i) within-study risk of bias due to high risk of bias; ii) publication bias could not be assessed; iii) imprecision due to small number of trials (one trial)

Summary of findings 7.   Gemcitabine plus oxaliplatin compared with 5-fluorouracil plus cisplatin plus radiotherapy for advanced biliary tract carcinomas

Gemcitabine plus oxaliplatin compared with fluorouracil plus cisplatin plus radiotherapy for advanced biliary tract carcinomas

Patient or population: people with advanced biliary tract carcinomas
Setting: specialist hospitals
Intervention: gemcitabine plus oxaliplatin
Comparison: fluorouracil plus cisplatin plus radiotherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with fluorouracil and cisplatin plus radio-therapy	**Risk with gemcitabine plus oxaliplatin**				
All-cause mortality at 1 year	Study population		RR 0.56 (0.21 to 1.52)	34 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	444 per 1000	249 per 1000 (93 to 676)				
Serious adverse events	Study population		RR 1.50 (0.66 to 3.39)	34 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	333 per 1000	500 per 1000 (220 to 1000)				
Health-related quality of life	Not reported					
Overall response rate	Not reported					
Time to progression of the tumour	Not reported					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RCT:** randomised clinical trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Summary of findings 8. Gemcitabine plus mitomycin C compared with capecitabine plus mitomycin C for advanced biliary tract carcinomas

Gemcitabine plus mitomycin C compared with mitomycin C plus capecitabine for advanced biliary tract carcinomas

Patient or population: people with advanced biliary tract carcinomas
Setting: specialist hospitals
Intervention: gemcitabine plus mitomycin C
Comparison: capecitabine plus mitomycin C

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of partici-pants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with capecitabine plus mitomycin C	Risk with gemcitabine plus mitomycin C				
All-cause mortality at 1 year	Study population		RR 1.14 (0.89 to 1.48)	51 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	769 per 1000	877 per 1000 (685 to 1000)				
Serious adverse events	Not reported					
Health-related quality of life	Not reported					
Overall response rate	Study population		RR 0.65 (0.25 to 1.72)	51 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	308 per 1000	200 per 1000 (77 to 529)				
Time to progression of the tu-mour	Not reported					
Grade 1 - 4 thrombocytopenia	Study population		RR 0.56 (0.29 to 1.06)	47 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1]	
	625 per 1000	350 per 1000 (181 to 663)				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded three levels (-3) because of i) within-study risk of bias due to high risk of bias; ii) publication bias could not be assessed; iii) imprecision due to small number of trials (one trial)

BACKGROUND

Description of the condition

Biliary tract cancers are a group of rare heterogeneous malignant tumours. They include intrahepatic and extrahepatic cholangiocarcinomas, gallbladder carcinomas, and ampullary carcinomas (De Groen 1999). Although these malignancies are anatomically related and have similar metastatic patterns, each has a distinct clinical presentation, molecular pathology, and prognosis (Zhu 2010; Nakanuma 2015; Jain 2016).

The incidence and mortality rates of biliary tract cancers has changed in the world since the mid-1980s. Population-based data from the Surveillance Epidemiology and End Results (SEER) Program showed an increase in the incidence and mortality of intrahepatic cholangiocarcinoma in the USA (Patel 2001; Shaib 2004; Welzel 2006). Similar trends were also observed in the UK between 1971 and 2001. In the British population, a 12-fold increase in the incidence of intrahepatic cholangiocarcinoma and a marked decrease in the incidence of gallbladder carcinoma and extrahepatic cholangiocarcinoma were observed during this period (West 2001). Consistent with these trends, there was a global trend of an increasing mortality from intrahepatic cholangiocarcinoma and decreasing mortality from extrahepatic cholangiocarcinoma, in industrialised countries and in low-income countries (Patel 2002).

Gallbladder carcinoma is the most common and most aggressive cancer of the biliary tract. Worldwide, there is a prominent geographic variability in gallbladder carcinoma incidence that correlates with the prevalence of gallbladder stones. High incidences of gallbladder carcinoma are seen in South American countries, particularly Chile, Bolivia, and Ecuador, as well as some areas of India, Pakistan, Japan, and Korea (Strom 1995; Randi 2006). Conditions that are associated with chronic inflammation of the gallbladder are considered risk factors for gallbladder carcinoma. These include gallstone disease, porcelain gallbladder, gallbladder polyps, chronic Salmonella infection, congenital biliary cysts, and abnormal pancreaticobiliary duct junction (Zhu 2010).

Cholangiocarcinoma accounts for only 3% of all gastrointestinal carcinomas (Venook 2011). Population-based incidence data on cholangiocarcinoma are scanty and most cancer registries combine people with cholangiocarcinoma with people with other hepatobiliary malignancies, such as hepatocellular cancer and gallbladder carcinoma (Patel 2002; Khan 2008). Although there are many established risk factors for cholangiocarcinoma including parasitic infections, primary sclerosing cholangitis, biliary-duct cysts, hepatolithiasis, toxins, and hepatitis viruses-related cirrhosis (for intrahepatic cholangiocarcinoma) (Tyson 2011), in most people with cholangiocarcinoma no predisposing factor is identified (Chapman 1999). The prognosis of cholangiocarcinoma is poor, and incidence and mortality are almost similar (Tyson 2011).

The ampulla of Vater consists of the terminal portion of the common bile duct and main pancreatic duct, as well as a small segment of the duodenal mucosa (Westgaard 2008). Because of its small size, adenocarcinomas are relatively uncommon in comparison with those arising in the pancreas or common bile duct. They account for only 0.5% of all gastrointestinal malignancies, and cancers of the ampulla of Vater are usually reported in case-controlled studies from single or collaborating institutions (Albores-Saavedra 2009). Although ampullary carcinomas are classified among biliary tract carcinomas, they are biologically and clinically distinct for their pathological, prognostic, and therapeutic features, and so the interpretation of study results in this specific patient subgroup have to be made cautiously.

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 (stage III) or metastatic (stage IV) disease, and they are only suitable for palliative chemotherapy or supportive care (Lamarca 2014). The prognosis for such people is generally poor, resulting in a five-year survival of 5% to 15% (Anderson 2004; DeOliveira 2007).

Description of the intervention

Chemotherapeutic agents have been studied extensively in advanced biliary carcinomas. Gemcitabine, either as a single agent or in combination with other chemotherapeutic agents, has been extensively evaluated in several phase II studies in people with advanced biliary tract carcinomas (Gebbia 2001; Kubicka 2001; Penz 2001). Overall, objective response with gemcitabine alone ranges from 7% to 27%, but median survival is only rarely longer than eight months (Park 2005; Suzuki 2010). One retrospective study of 304 people with unresectable biliary tract carcinoma compared the outcome for people who received gemcitabine alone to people who received a cisplatin-based regimen, a fluoropyrimidine-based regimen, or best supportive care. Gemcitabine seemed to be the most effective treatment, with a reduction in mortality of about 50% when compared with best supportive care (Yonemoto 2007). The results of a pooled analysis of 104 trials that included 2810 people with advanced biliary tract carcinoma showed that response and tumour control were higher for the subgroup of people who received gemcitabine and platinum-based agents. However, this tumour response did not translate into significant benefit in terms of either time to tumour progression or median overall survival (Eckel 2007; Eckel 2014).

The superiority of gemcitabine plus cisplatin over gemcitabine alone was shown in the randomised clinical phase III multicentre ABC-02 trial, which enrolled 410 people with locally-advanced or metastatic cholangiocarcinoma, gallbladder carcinoma, or ampullary carcinoma. Participants were randomly assigned to six courses of cisplatin (25 mg/m^2) followed by gemcitabine (1000 mg/m^2) on days one and eight, every 21 days, versus gemcitabine alone (1000 mg/m^2 on days one, eight, and 15 every 28 days). At a median follow-up of 8.2 months, overall survival was significantly longer with gemcitabine plus cisplatin therapy (11.7 months with gemcitabine plus cisplatin versus 8.1 months gemcitabine alone), as well as median progression-free survival (eight months with gemcitabine plus cisplatin versus five months with gemcitabine alone). The proportion of participants with neutropenia was higher in the group receiving gemcitabine plus cisplatin. However, there was no significant difference in the proportion with neutropenia-associated infections between the two treatment groups (Valle 2010; Valle 2014). Another smaller randomised clinical trial with 84 people with advanced biliary tract carcinoma reported a similar conclusion with a significantly longer overall survival with cisplatin plus gemcitabine compared with gemcitabine alone (11.2 months with gemcitabine plus cisplatin versus 7.7 months with

gemcitabine alone) (Okusaka 2010). Other treatments which have been evaluated (with gemcitabine or compared to gemcitabine-based regimens) include other chemotherapeutics (e.g. cisplatin, carboplatin, fluoropyrimidines) and localised radiotherapy in combination with concurrent chemotherapy (for peoples with locally-advanced disease) (Chen 2016). Additionally, alternative therapeutic strategies besides systemic chemotherapy have been suggested, mainly for intrahepatic cholangiocarcinoma including intra-arterial chemotherapy, radioembolisation, and immune therapy (Schweitzer 2015). There is as yet no level-I evidence of a survival benefit for targeted therapy in advanced biliary tract carcinomas (Chen 2016)

How the intervention might work

Gemcitabine is a cell-cycle phase-specific chemotherapeutic agent. It primarily kills cells undergoing deoxyribonucleic acid (DNA) synthesis (S-phase) as well as blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolised intracellularly to the active diphosphate and triphosphate nucleotides. The cytotoxic effect of gemcitabine is due to a combination of the two actions by the diphosphate and the triphosphate nucleotides leading to inhibition of DNA synthesis (Mini 2006).

Gemcitabine has shown biological activities in a broad spectrum of solid tumours, including pancreatic cancers (Burris 1997). Because the biliary tract shares a common embryological origin with the exocrine pancreas, gemcitabine was considered as a reasonable therapeutic agent to be evaluated for the treatment of biliary tract cancers (Park 2005).

Why it is important to do this review

For advanced biliary tract carcinoma, systemic therapy is the mainstay of treatment for people who present with unresectable or metastatic disease. Progress has been made since the mid-2000s to identify the most effective chemotherapy regimens, with the recent recommendation of the combination of gemcitabine plus cisplatin as the standard schedule. This is based on the results of the ABC-02 trial (Valle 2010), and the identically-designed Japanese trial (Okusaka 2010). Both trials demonstrated a significantly longer overall survival with gemcitabine plus cisplatin compared with gemcitabine alone. However, gemcitabine plus cisplatin has not been directly compared with other non-gemcitabine-containing chemotherapy combinations in phase III trials. Comprehension of the molecular basis of cholangiocarcinogenesis and tumour progression has led to the testing of other chemotherapies in people with biliary tract carcinomas, demonstrating promising results (Marino 2013; Schweitzer 2015; Chen 2016). Although gemcitabine plus cisplatin is considered a standard option for advanced biliary cancer, exploration of other systemic therapy regimens in people with advanced biliary tract carcinomas is still needed, in order to improve outcomes for this disease. Moreover, the population of biliary tract carcinomas is heterogeneous, and because the incidence of biliary tract carcinoma is low, people with unresectable, metastatic or recurrent cancers are often enrolled in the same randomised clinical trial. Thus, the efficacy of gemcitabine-based chemotherapy in all clinical contexts and anatomical subsites needs detailed assessment.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

All randomised clinical trials, irrespective of language or publication status, comparing intravenous administration of gemcitabine monotherapy or gemcitabine-based combination therapy compared to placebo, to no intervention, or to treatments other than gemcitabine. We examined non-randomised studies retrieved with the searches for harmful effects only. We are aware that this may bias our review towards assessing benefits rather than harms.

Types of participants

All chemotherapy-naïve people with cytological or histopathological evidence of advanced (either unresectable or metastatic) biliary tract carcinomas (i.e. intra- and extrahepatic cholangiocarcinoma, gallbladder carcinoma, and ampullary carcinoma) who are without clinical evidence of active or former concurrent malignant diseases, and are older than 18 years. The definition of unresectable biliary tract carcinomas was according to the authors of the individual trials.

Types of interventions

Intravenous gemcitabine (monotherapy or combination therapy) versus placebo or no treatment, or treatments other than gemcitabine:

- gemcitabine-based chemotherapy versus placebo or no intervention;
- gemcitabine-based chemotherapy versus chemotherapy without gemcitabine.

Types of outcome measures

Primary outcomes

- All-cause mortality.
- Serious adverse events. We used the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice's definition of a serious adverse event (ICH-GCP 1997); that is, any untoward medical occurrence that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. We considered all other adverse events as non-serious (see below).
- Health-related quality of life: if reported in individual trials by the participants and if measured with validated instruments.

Secondary outcomes

- Tumour response assessments (as recommended by the response evaluation in solid tumours criteria) using the following definitions of response (Eisenhauer 2009):
  - complete response: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than 10 mm;
  - partial response: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters;
  - progressive disease: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression;
  - stable disease: neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

We combined complete response and partial response to evaluate the overall response rate. However, alternative criteria could have been added according to the choice of the trial authors.

- Time to progression of the tumour (reported as median time to progression).
- (Non-serious) adverse events.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2018; June 2017), Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2017, Issue 5), MEDLINE Ovid (1946 to June 2017), Embase Ovid (1974 to June 2017), LILACS (Bireme; 1982 to June 2017), Science Citation Index Expanded (Web of Science; 1900 to June 2017), and Conference Proceedings Citation Index – Science (Web of Science; 1990 to June 2017) (Royle 2003). Appendix 1 shows the search strategies used for the electronic searches. We also searched the www.clinicaltrials.gov register for additional studies and for ongoing studies. We added these to Characteristics of ongoing studies.

Searching other resources

We manually checked reference lists of the included studies and review articles for more trials of interest (cross-references).

Data collection and analysis

We conducted the review according to recommendations of Cochrane (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2018). We performed the analyses using Review Manager 5 (RevMan 2014).

Selection of studies

Independently of each other, we identified the trials for inclusion. We have listed the excluded studies with the reasons for exclusion.

We excluded duplicate records based on consideration of titles and abstracts. We reviewed abstracts of the remaining articles. We conducted a review of the remaining articles for relevancy and reporting of outcomes of interest.

Data extraction and management

We individually extracted the required data. We extracted details of study population, interventions, and outcomes using a standardised data extraction form. This form included the following items:

- publication year;
- country;
- year of conduct of the trial;
- inclusion and exclusion criteria;
- sample size calculation performed or not;
- population characteristics, such as age and sex ratio;
- sample size reached or not;
- baseline characteristics including: Eastern Cooperative Oncology Group Performance Status; stage; and primary subsite of the tumour: intrahepatic and extrahepatic cholangiocarcinomas, gallbladder carcinomas, and ampullary carcinomas;
- outcomes (see Primary outcomes; Secondary outcomes);
- risk of bias (see Assessment of risk of bias in included studies);
- intention-to-treat analysis.

Assessment of risk of bias in included studies

Due to the risk of overestimation of beneficial intervention effects and underestimation of harmful intervention effects in randomised clinical trials of unclear or inadequate methodological quality (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017), we assessed the influence of the risks of bias on our results. We used the domains with definitions provided below to assess the risks of bias in the included trials (Higgins 2011; Gluud 2018). In our assessment of the risks of bias, we included assessments of available information included in trial registrations unless the trial was registered after the trial was completed.

Allocation sequence generation (selection bias)

- Low risk of bias: sequence generation was achieved using computer random-number generation or a random-number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Unclear risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random. We included such studies only for assessments of harms.

Allocation concealment (selection bias)

- Low risk of bias: the participant allocations could not have been foreseen in advance of or during enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators

(e.g. if the allocation sequence was hidden in sequentially-numbered, opaque, and sealed envelopes).

- Unclear risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of or during enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants. We included such studies only for assessments of harms.

Blinding of participants and personnel (performance bias)

- Low risk of bias: it was mentioned that both the participants and personnel providing the interventions were blinded, and the method of blinding was described, so that knowledge of allocation was prevented during the trial.
- Unclear risk of bias: it was not mentioned if the trial was blinded, or the trial was described as blinded, but the method or extent of blinding was not described, so that knowledge of allocation was possible during the trial.
- High risk of bias: the trial was not blinded, so that the allocation was known during the trial. We included such studies only for assessments of harms.

Blinding of outcome assessment (detection bias)

- Low risk of bias: outcome assessment was carried out blinded for all relevant outcomes, and the method of blinding was described, so that knowledge of allocation was prevented.
- Unclear risk of bias: blinding of outcome assessment was not described, or the outcome assessment was described as blinded, but the method of blinding was not described, so that knowledge of allocation was possible.
- High risk of bias: outcome assessment was not blinded, so that the allocation was known to outcome assessors. We included such studies only for assessments of harms.

Incomplete outcome data (attrition bias)

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, were employed to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias in the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting (reporting bias)

- Low risk: the trial reported the following predefined outcomes: all-cause mortality, serious adverse events, and tumour response (see Secondary outcomes). When the original trial protocol was available, the outcomes were those called for in that protocol. When the trial protocol was obtained from a trial registry (e.g. www.clinicaltrials.gov), the outcomes sought were those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, we did not consider those outcomes to be reliable.
- Unclear risk: not all predefined outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk: one or more predefined outcomes were not reported.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support that may manipulate the trial design, conduct or results.
- Unclear risk of bias: the trial may or may not be free of for-profit bias, as no information on clinical trial support or sponsorship was provided.
- High risk of bias: the trial was sponsored by industry or received other type of for-profit support.

Other bias

- Low risk of bias: the trial appeared to be free of other factors that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not have been free of other factors that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias. We included such studies only for assessments of harms.

We judged trials to be at low overall risk of bias if rated as low risk of bias in all the above domains. We judged trials to be at high overall risk of bias if rated as unclear risk of bias or high risk of bias in one or more of the above domains.

We resolved any differences in opinion through discussion; in the case of unsettled disagreements, we planned to ask a member of the Cochrane Hepato-Biliary Group Editorial Team Office to adjudicate.

Measures of treatment effect

For dichotomous variables, we calculated the risk ratio (RR) with a 95% confidence interval (CI). For continuous variables, we planned to calculate the mean difference (MD) or standardised mean difference (SMD) with its 95% CI. Time-to-event data analyses are usually based on hazard ratios (HRs), so if these data were provided we planned to use the HR. If HR data were not provided, we planned to calculate the ln(HR) and its standard error indirectly, or we planned to use an Excel spreadsheet to obtain the exact HR (Parmar 1998).

Unit of analysis issues

The unit of analysis is the group of participants in each intervention group in the randomised clinical trials with a parallel-group design. In the case of cross-over trials, we used the data from the first trial period only. In case of trials with more than two intervention groups, we produced two different analyses, comparing the intervention group with the common control group.

Dealing with missing data

When we could not extract data from the text, we contacted the authors of the original publication to ask for missing information.

Intention-to-treat analyses

For the primary outcomes, we planned to include participants with incomplete or missing data in sensitivity analyses by imputing them according to the following scenarios (Hollis 1999):

- Extreme case analysis favouring the experimental intervention ('best-worse' case scenario): none of the dropouts/participants

lost from the experimental group, but all of the dropouts/participants lost from the control group experienced the outcome; we included all randomised participants in the denominator;

- Extreme case analysis favouring the control ('worst-best' case scenario): all dropouts/participants lost from the experimental group, but none from the control group experienced the outcome; we included all randomised participants in the denominator.

However, because there was a low risk of attrition bias in most of the included trials, we did not do these analyses.

Assessment of heterogeneity

We used the Chi^2 test to provide an indication of between-trial heterogeneity. In addition, we quantified the degree of heterogeneity observed in the results using the I^2 statistic, which can be interpreted as the percentage of variation observed between the trials attributable to between-trial differences rather than sampling error (chance).

We interpreted I^2 values as follows:

- probably not important: 0% to 40%;
- possible moderate heterogeneity: 30% to 60%;
- possible substantial heterogeneity: 50% to 90%;
- considerable heterogeneity: 75% to 100% (Higgins 2011).

Assessment of reporting biases

We carried out a comprehensive search in order to minimise the risk of publication bias. Because we did not identify enough trials for inclusion (10 trials), we did not use a funnel plot to explore bias (Egger 1997; Macaskill 2001).

Data synthesis

The review authors followed the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2018).

Meta-analysis

We used random-effects model (DerSimonian 1986) and fixed-effect model (Mantel 1959; DeMets 1987) meta-analyses. In case of discrepancy between the two models (e.g. one giving a significant intervention effect, and the other no significant intervention effect), we reported both results; otherwise, we reported only the results from the meta-analysis model with the most conservative intervention effect (Jakobsen 2014).

Trial Sequential Analysis

We examined intervention effects with Trial Sequential Analysis (TSA) (Thorlund 2011; TSA 2011; Wetterslev 2017), in order to evaluate if intervention effects could be caused by random error ('play of chance') (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009, Wetterslev 2009; Thorlund 2010). However, we found TSA only suitable for one comparison out of the seven comparisons of the review.

We applied Trial Sequential Analysis as cumulative meta-analyses are at risk of producing random errors due to sparse data and repetitive testing of the accumulating data (Wetterslev 2008). To

control for random errors, we calculated the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect). The required information size calculation should also account for the diversity present in the meta-analysis (Wetterslev 2009). In our meta-analysis, the diversity-adjusted required information size was based on the event proportion in the control group; assumption of a plausible risk ratio reduction of 20% or the risk ratio reduction observed in the included trials at low risk of bias; a risk of type I error of 2.5%, a risk of type II error of 10%, and the assumed diversity of the meta-analysis. The underlying assumption of Trial Sequential Analysis is that testing for significance may be performed each time a new trial is added to the meta-analysis. We added the trials according to the year of publication, and, if more than one trial was published in a year, we added trials alphabetically according to the last name of the first author. On the basis of the diversity-adjusted required information size, we constructed trial sequential monitoring boundaries (Wetterslev 2008; Thorlund 2011). These boundaries determine the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the required information size; if the cumulative Z-curve crosses the trial sequential monitoring boundary for benefit or harm before the diversity-adjusted required information size is reached, firm evidence may perhaps be established and further trials may be superfluous. On the contrary, if the boundary is not surpassed, it is most probably necessary to continue doing trials in order to detect or reject a certain intervention effect. That can be determined by assessing if the cumulative Z-curve crosses the trial sequential monitoring boundaries for futility.

Subgroup analysis and investigation of heterogeneity

We planned to perform a subgroup analysis comparing the intervention effect in:

- trials at low risk of bias compared to trials at high risk of bias;
- Eastern Cooperative Oncology Group Performance Score 0 compared to score 1 or 2;
- tumour site (cholangiocarcinoma, gallbladder carcinoma, ampullary carcinoma);
- tumour stage.

However, because of insufficient trial data, we could not perform all these subgroup analyses.

Sensitivity analysis

To assess the robustness of the eligibility criteria, in addition to the sensitivity analyses specified under Dealing with missing data, we planned to undertake sensitivity analyses that may explain our findings, including any observed heterogeneity. However, because of missing data, we could not perform this sensitivity analysis.

'Summary of findings' tables

We created 'Summary of findings' tables using GRADEpro (GRADEpro 2008; Table 1). We used the GRADE approach which appraises the certainty of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The certainty of evidence considers within-study risk of bias, indirectness of the evidence (population, intervention, control, outcomes), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of results (wide CIs

as evaluated with Trial Sequential Analyses) (Jakobsen 2014), and risk of publication bias (Balshem 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Guyatt 2013d; Mustafa 2013; Guyatt 2017).

These grades are defined as follows.

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

R E S U L T S

Description of studies

Results of the search

We identified 3161 records from our database searches (Figure 1). Among the identified 3161 records, the number of duplicates that

we found and removed was 620 records. Thus, the final number of records that we scanned was 2541. Based on the titles and abstracts of these records, we excluded 2521 records and further assessed the retrieved full-text paper publications of the remaining 20 records (Figure 1). We found seven randomised clinical trials described in seven publications which fulfilled the inclusion criteria of our systematic review (Kornek 2004; Sharma 2010; Kang 2012; Morizane 2013; Phelip 2014; Santoro 2015; Li 2016). Co-interventions (other than gemcitabine) were equally applied in three trials (Morizane 2013: gemcitabine plus S-1 versus S-1 alone; Santoro 2015: gemcitabine plus vandetanib versus vandetanib alone; Li 2016: gemcitabine plus S-1 versus S-1 alone), while in the other four trials co-interventions were unequally applied (Kornek 2004: gemcitabine plus mitomycin C versus capecitabine plus mitomycin C; Sharma 2010: gemcitabine plus oxaliplatin versus 5-fluorouracil plus folinic acid versus best supportive care; Kang 2012: gemcitabine plus cisplatin versus S-1 plus cisplatin; Phelip 2014: gemcitabine plus oxaliplatin versus chemoradiotherapy protocol). The trials were set in single countries, conducted in India, Japan, France, Austria, South Korea, China, and Italy. The median age in the seven trials varied between 50 and 60 years and the numbers of included men and women were comparable in most of the trials. All the included trials were parallel-group trials.

Figure 1. Study flow diagram


```
┌─────────────────────┐
│ 3161 records        │          ┌──────────────────────────┐
│ identified through  │─────────▶│ 620 duplicate records    │
│ database            │          │ removed                  │
│ searching and       │          └──────────────────────────┘
│ other sources       │
└─────────────────────┘
          │
          ▼
┌─────────────────────┐          ┌──────────────────────────┐
│ 2541 records        │─────────▶│ 2521 records             │
│ screened            │          │ excluded                 │
└─────────────────────┘          └──────────────────────────┘
          │
          ▼
┌─────────────────────┐          ┌──────────────────────────┐
│ 20 records          │          │ 13 records (13           │
│ assessed for        │─────────▶│ studies) excluded        │
│ eligibility         │          │ because of not           │
└─────────────────────┘          │ fulfilling inclusion     │
          │                      │ criteria                 │
          ▼                      └──────────────────────────┘
┌─────────────────────┐
│ 7 records (7         │
│ randomised           │
│ clinical trials)     │
│ included in          │
│ qualitative and      │
│ quantitative         │
│ synthesis            │
└─────────────────────┘
```
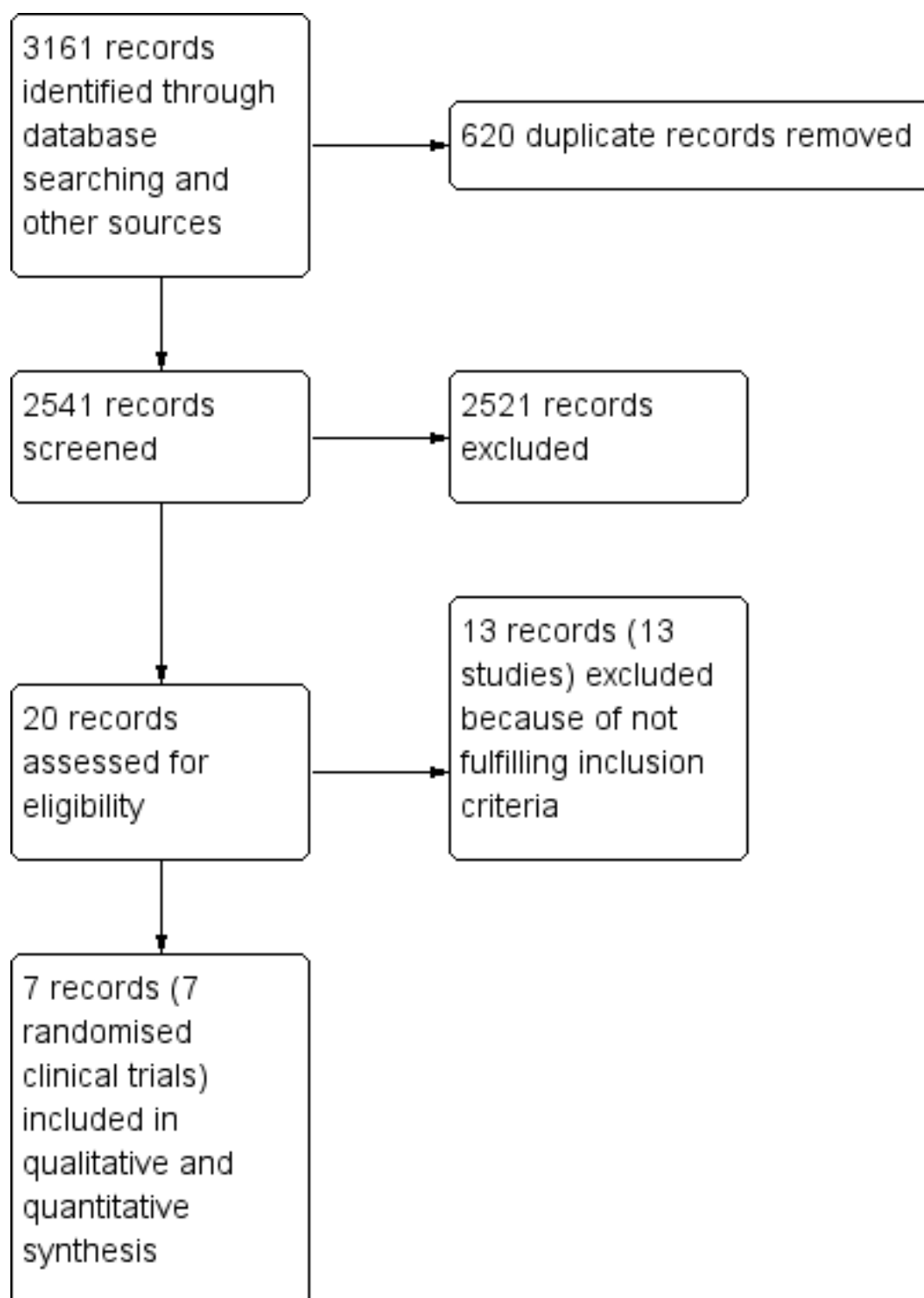
We excluded the remaining 13 publications as they did not fulfil the inclusion criteria of our review (Raderer 1999; Valle 2009; Okusaka 2010; Valle 2010; Lee 2012; Sasaki 2013; Malka 2014; Moehler 2014; Wan 2014; Chen 2015; Lee 2015; Valle 2015; Leone 2016). We also found three ongoing randomised trials of interest to our review (NCT01470443; NCT02591030; NCT03044587).

Included studies

Included studies

We included seven studies with a total of 600 participants in this systematic review (Characteristics of included studies).

Santoro 2015 randomised 173 participants (recruited from October 2008 to September 2012) at 19 centres across Italy. The trial participants were randomised in a 1:1:1 ratio to three treatment groups: a comparator group of vandetanib 300 mg monotherapy (group A), two intervention groups of vandetanib 100 mg plus gemcitabine (group B), and gemcitabine plus placebo (group C). Planned outcomes were progression-free survival, overall survival, response rate, disease control rate, duration of response, performance status and safety outcomes. For data analysis purposes, both the gemcitabine plus vandetanib group and the gemcitabine plus placebo group were considered as the experimental intervention groups, and outcomes from each of these groups were compared against the vandetanib monotherapy (i.e. non-gemcitabine-containing comparator) control group.

Kang 2012 randomised 96 participants (enrolled from March 2008 to March 2009); 49 participants were randomised to the experimental intervention (gemcitabine (1000 mg/m^2 IV at 10 mg/m^2/min on days 1 and 8) and cisplatin (60 mg/m^2 intravenously (IV) on day 1) every three weeks) and 47 participants to the control intervention (S-1 (40 mg/m^2 orally twice a day on days 1 and 14) plus cisplatin (60 mg/m^2 IV on day 1). Planned outcomes were progression-free survival, response rate, overall survival, and toxicity.

Morizane 2013 randomised 101 participants (from February 2009 to April 2010) to an experimental intervention of gemcitabine (gemcitabine: 1000 mg/m^2, day 1 and day 8; S-1: 60 mg/m^2, twice daily on days 1 and 14, repeated every three weeks plus S-1 (a combination of tegafur, gimeracil, and oteracil); and a control intervention of S-1 (80 mg/m^2, days 1 to 28, given orally twice daily for four weeks, followed by a two-week rest, repeated every six weeks). Planned outcomes were progression-free survival, overall survival, response rate in participants with measurable lesions, the incidences of adverse events, and serious adverse events.

Li 2016 randomised 75 participants to three treatment groups: two control intervention groups of S-1 monotherapy (orally twice daily for 14 days, followed by a 14-day rest: group A) and gemcitabine monotherapy (1000 mg/m^2 intravenously over 30 minutes on days 1, 8, and 15: group B), and one experimental intervention group of gemcitabine (in the same dose) plus S-1: group C. All participants were treated within a four-week cycle. Planned outcomes were overall survival, progression-free survival, objective response rate, and safety of chemotherapeutic agents. For data analysis purposes, the (gemcitabine/S-1) group was considered as the intervention group and we compared outcomes from this group against the S-1 monotherapy group (i.e. non-gemcitabine-containing comparator). We excluded the third group of gemcitabine/placebo from the analysis, following our protocol.

Sharma 2010 randomised 81 participants (from June 2006 to October 2008) into three groups, including two control intervention groups (group A: best supportive care (27 participants); group B: 5-fluorouracil and folinic acid (28 participants)), and an experimental intervention group (group C: gemcitabine plus oxaliplatin (26 participants)), for a maximum of six cycles. Planned outcomes included progression-free survival, response rate, overall survival, and toxicity patterns. For our analysis, we divided the intervention group into two equal halves and compared each half with a different comparator group.

Phelip 2014 randomised 34 participants (between July 2006 and December 2010) with locally-advanced biliary tract cancers to an experimental intervention (16 participants in the gemcitabine-based chemotherapy group) and control intervention (18 participants in the chemoradiotherapy group). Chemoradiotherapy consisted of 5-fluorouracil infusion and cisplatin, and was given in association with radiotherapy (50 Gy), while gemcitabine-based chemotherapy consisted of gemcitabine combined with oxaliplatin (GEMOX) for six months. Planned outcomes were overall progression-free survival, overall survival, toxicity, rate of biliary complications, and duration of hospitalisation.

Kornek 2004 randomised 51 participants (enrolment dates were not reported in the published paper) to group A (experimental intervention): mitomycin C 8 mg/m^2 on day 1 in combination with gemcitabine 2000 mg/m^2 on days 1 and 15 every four weeks; or group B (control intervention): mitomycin C 8 mg/m^2 on day 1 plus capecitabine 2000 mg/m^2/day on days 1 and 14, every four weeks. In both groups, chemotherapy was administered for six months, unless progression of disease occurred earlier. Planned outcomes were progression-free survival, response rate, overall survival, and treatment tolerance.

Excluded studies

We excluded 13 studies, as they did not fulfil our inclusion criteria (Characteristics of excluded studies). In Raderer 1999 study, the results of the prospectively-enrolled participants to the gemcitabine group were retrospectively compared to a patient cohort treated with 5-fluorouracil, leucovorin (LV) plus mitomycin C. Lee 2015 was a retrospective analysis of clinical data through reviewing medical records to compare the efficacy of gemcitabine-cisplatin versus capecitabine-cisplatin combination chemotherapy. In the three UK ABC trials (Valle 2009; Valle 2010; Valle 2015), gemcitabine was used in both groups of each of the three randomised trials. Similarly, the trials of Okusaka 2010; Lee 2012; Sasaki 2013; Malka 2014; Moehler 2014; Wan 2014; Chen 2015 and Leone 2016 used gemcitabine in both randomised groups of the trial.

Risk of bias in included studies

For graphical presentation of risk of bias of the included trials, see Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.
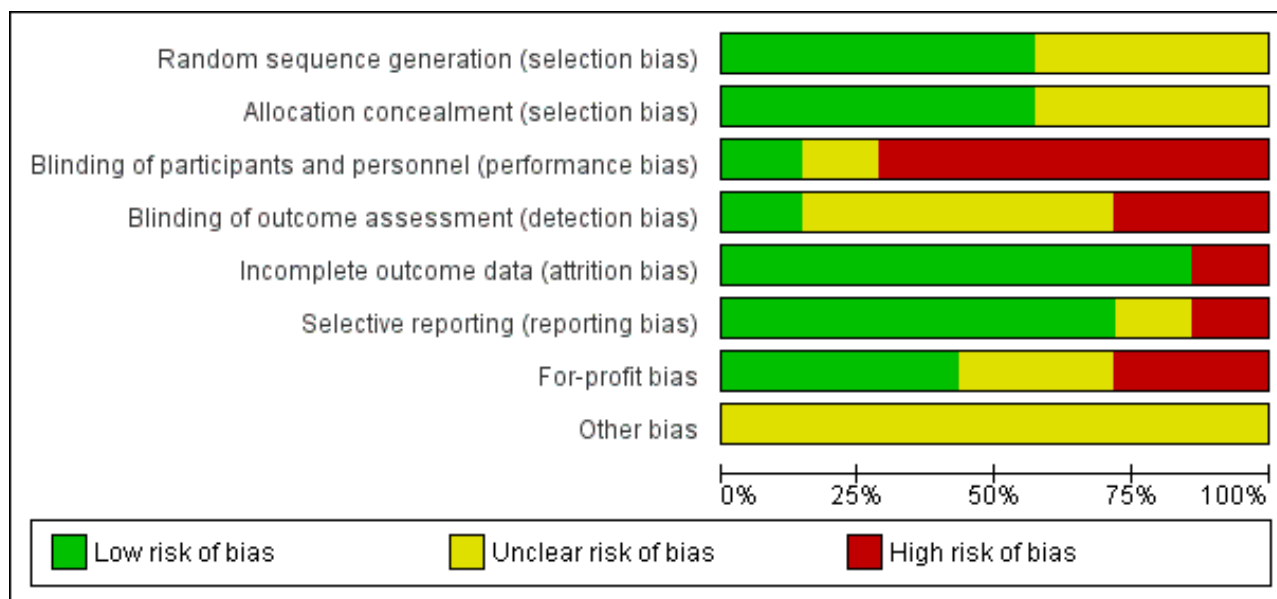
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

Allocation

Both allocation sequence generation and allocation concealment were clearly reported in four trials (Kornek 2004; Morizane 2013; Santoro 2015; Li 2016), while it was unclear in three trials (Sharma 2010; Kang 2012; Phelip 2014).

Blinding

Blinding of participants and personnel was clearly reported in the Santoro 2015 trial; unclearly reported in the Kornek 2004 trial; with a high risk of performance bias in Sharma 2010; Kang 2012; Morizane 2013; Phelip 2014 and Li 2016. Blinding of outcome assessment was clearly reported in the Santoro 2015 trial; unclearly

reported by Kornek 2004; Kang 2012 and Phelip 2014; with a high risk of detection bias in Morizane 2013 and Li 2016.

Incomplete outcome data

There was a low risk of attrition bias in all included trials except for Li 2016, where we rated the risk of attrition bias as high.

Selective reporting

There was a low risk of reporting bias in all the included trials except for Phelip 2014, where we rated the risk of reporting bias as high, and except for Santoro 2015 where we rated the risk of reporting bias as unclear.

For-profit bias

There was a high risk of for-profit bias in Phelip 2014 and Santoro 2015 (because of industry sponsorship), while there was a low risk of for-profit bias in Kang 2012; Morizane 2013 and Li 2016, and unclear risk in Kornek 2004 and Sharma 2010 trials.

Other potential sources of bias

We found no evidence of other biases in the included trials.

Overall, we assessed all of the included trials at high risk of bias in at least one of the above domains; thus, all trials were considered at high overall risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Gemcitabine plus vandetanib compared with vandetanib for advanced biliary tract carcinomas; **Summary of findings 2** Gemcitabine versus vandetanib for advanced biliary tract carcinomas; **Summary of findings 3** Gemcitabine plus cisplatin compared with S-1 plus cisplatin for advanced biliary tract carcinomas; **Summary of findings 4** Gemcitabine plus S-1 compared with S-1 for advanced biliary tract carcinomas; **Summary of findings 5** Gemcitabine plus oxaliplatin compared with best supportive care for advanced biliary tract carcinomas; **Summary of findings 6** Gemcitabine plus oxaliplatin compared with 5-fluorouracil plus folinic acid for advanced biliary tract carcinomas; **Summary of findings 7** Gemcitabine plus oxaliplatin compared with 5-fluorouracil plus cisplatin plus radiotherapy for advanced biliary tract carcinomas; **Summary of findings 8** Gemcitabine plus mitomycin C compared with capecitabine plus mitomycin C for advanced biliary tract carcinomas

1. Gemcitabine plus vandetanib versus vandetanib alone

One trial included data related to this comparison (Santoro 2015).

All-cause mortality

There was no mention of all-cause mortality in any of the groups of this comparison.

Health-related quality of life

There was no mention of health-related quality of life in any of the groups of this comparison.

Serious adverse events

In Santoro 2015, we found no overt differences between the treatment groups in the proportion of participants who experienced serious adverse events (16 participants (27.1%) in the vandetanib monotherapy group and 15 participants (25.9%) in the gemcitabine/vandetanib combination group). Types of serious adverse events reported in this trial included hepatic toxicities, haematological toxicities, and infections. Risk ratio (RR) for the probability of serious adverse events was 0.95 (95% confidence interval (CI) 0.52 to 1.74; P = 0.88; participants = 117; Analysis 1.1), favouring neither gemcitabine nor non-gemcitabine regimens.

Time to progression of the tumour (reported as median time to progression)

There was no mention of time to progression of the tumour in any of the groups of this comparison.

Tumour response assessments

Tumour response was evaluated in accordance with the response evaluation in solid tumours criteria in this comparison. The RR for overall response rate (combination of complete response with partial response) was 5.40 (95% CI 1.25 to 23.29; P = 0.02; participants = 117; Analysis 1.2), favouring the gemcitabine-based regimen. Overall response rate was not stratified in this trial by tumour site, tumour stage, or performance status.

Non-serious adverse events

Non-serious adverse events were categorised in all the included trials according to the National Cancer Institute common terminology criteria (NCI-CTC 2016), and we ranked them accordingly into grades one to four.

RR for all grades of anaemia (grade 1 - 4) was 7.12 (95% CI 0.90 to 56.08; P = 0.06; participants = 117; Analysis 1.3), favouring neither gemcitabine nor non-gemcitabine regimens.
RR for high-grade anaemia (grade 3 - 4) was 3.05 (95% CI 0.13 to 73.39; P = 0.49; participants = 117; Analysis 1.4), favouring neither gemcitabine nor non-gemcitabine regimens.
RR for all grades of neutropenia (grade 1 - 4) was 15.25 (95% CI 0.89 to 261.11; P = 0.06; participants = 117; Analysis 1.5), favouring neither gemcitabine nor non-gemcitabine regimens.
RR for high-grade neutropenia (grade 3 - 4) was 9.15 (95% CI 0.50 to 166.27; P = 0.13; participants = 117; Analysis 1.6), favouring neither gemcitabine nor non-gemcitabine regimens.

2. Gemcitabine versus vandetanib

One trial included data related to this comparison (Santoro 2015).

All-cause mortality

There was no mention of all-cause mortality in any of the groups of this comparison.

Health-related quality of life

There was no mention of health-related quality of life in any of the groups of this comparison.

Serious adverse events

In Santoro 2015, we found no overt differences between the treatment groups in the proportion of participants who experienced serious adverse events (12 participants in the gemcitabine monotherapy group and 16 participants in the vandetanib monotherapy group). The RR for the probability of serious adverse events was 0.79 (95% CI 0.41 to 1.52; P = 0.48;

participants = 115; Analysis 2.1), favouring neither gemcitabine nor non-gemcitabine regimens.

Time to progression of the tumour (reported as median time to progression)

There was no mention of time to progression of the tumour in any of the groups of this comparison.

Tumour response assessments

Tumour response was evaluated in accordance with the response evaluation in solid tumours criteria in this comparison. The RR for overall response rate (combination of complete response with partial response) was 3.77 (95% CI 0.82 to 17.33; P = 0.09; participants = 108; Analysis 2.2), favouring neither gemcitabine nor non-gemcitabine regimens. Overall response rate was not stratified in this trial by tumour site, tumour stage, or performance status.

Non-serious adverse events

Non-serious adverse events were categorised according to the National Cancer Institute common terminology criteria (NCI-CTC 2016), and we ranked them accordingly into grades one to four.

RR for all grades of anaemia (grade 1 - 4) was 7.38 (95% CI 0.94 to 58.05; P = 0.06; participants = 115; Analysis 2.3), favouring neither gemcitabine nor non-gemcitabine regimens.
RR for high-grade anaemia (grade 3 - 4) was 3.16 (95% CI 0.13 to 75.94; P = 0.48; participants = 115; Analysis 2.4), favouring neither gemcitabine nor non-gemcitabine regimens.
RR for all grades of neutropenia (grade 1 - 4) was 22.11 (95% CI 1.33 to 368.56; P = 0.03; participants = 115; Analysis 2.5), favouring neither gemcitabine nor non-gemcitabine regimens.
RR for high-grade neutropenia (grade 3 - 4) was 11.58 (95% CI 0.66 to 204.68; P = 0.09; participants = 115; Analysis 2.6), favouring neither gemcitabine nor non-gemcitabine regimens.

3. Gemcitabine plus cisplatin versus S-1 plus cisplatin

One trial contributed data related to this comparison (Kang 2012).

All-cause mortality

The RR for all-cause mortality at one year was 0.76 (95% CI 0.58 to 0.98; P = 0.04; participants = 96; Analysis 3.1), favouring gemcitabine-based chemotherapy. All-cause mortality was not stratified by tumour site, tumour stage, or performance status. In Kang 2012, all-cause mortality was reported in the text at eight months, and we extracted the one-year mortality from the survival curve in order for the result to be consistent with all-cause mortality from other comparisons.

Health-related quality of life

There was no mention of health-related quality of life in any of the groups of this comparison.

Serious adverse events

There was no mention of serious adverse events in any of the groups of this comparison.

Time to progression of the tumour (reported as median time to progression)

There was no mention of time to progression of the tumour in any of the groups of this comparison.

Tumour response assessments

Tumour response was evaluated in accordance with the response evaluation in solid tumours criteria in this comparison. The RR for overall response rate (complete response and partial response) was 0.82 (95% CI 0.37 to 1.82; P = 0.63; participants = 88; Analysis 3.2), favouring neither gemcitabine nor non-gemcitabine regimens. Overall response rate was not stratified in this trial by tumour site, tumour stage, or performance status.

Non-serious adverse events

Non-serious adverse events were categorised in all the included trials according to the National Cancer Institute common terminology criteria (NCI-CTC 2016), and we ranked them accordingly into grades one to four.

RR for all grades of anaemia (grade 1 - 4) was 11.27 (95% CI 4.41 to 28.83; P < 0.001; participants = 96; Analysis 3.3), favouring non-gemcitabine-based regimens.
RR for high-grade anaemia (grade 3 - 4) was 10.55 (95% CI 1.42 to 78.56; P = 0.02; participants = 96; Analysis 3.4), favouring non-gemcitabine regimens.
RR for all grades of thrombocytopenia (grade 1 - 4) was 6.71 (95% CI 2.55 to 17.68; P < 0.001; participants = 96; Analysis 3.5), favouring non-gemcitabine regimens.
RR for high-grade thrombocytopenia (grade 3 - 4) was 5.28 (95% CI 1.23 to 22.55; P = 0.02; participants = 96; Analysis 3.6), favouring non-gemcitabine regimens.
RR for all grades of neutropenia (grade 1 - 4) was 1.28 (95% CI 0.95 to 1.72; P = 0.11; participants = 96; Analysis 3.7), favouring neither gemcitabine nor non-gemcitabine regimens.
RR for high-grade neutropenia (grade 3 - 4) was 1.64, 95% CI 0.97 to 2.78 ; P = 0.06; Analysis 3.8), favouring neither gemcitabine nor non-gemcitabine regimens.
RR for febrile neutropenia was 4.80 (95% CI 0.24 to 97.42 ; P = 0.31; participants = 96; Analysis 3.9), favouring neither gemcitabine nor non-gemcitabine regimens.

4. Gemcitabine plus S-1 versus S-1

Two trials included data related to this comparison (Morizane 2013; Li 2016).

All-cause mortality

The RR for all-cause mortality at one year was 0.61 (95% CI 0.33 to 1.13; P = 0.12; participants = 151; trials = 2; I² = 76% (significant heterogeneity); Analysis 4.1), favouring neither gemcitabine nor non-gemcitabine-based chemotherapy. All-cause mortality was not stratified in this trial by tumour site, tumour stage, or performance status. In both trials, all-cause mortality was reported at one year. In order to detect or reject a risk reduction of 20%, the diversity-adjusted required information size was n = 2655 trial participants, based upon a proportion of death of 70% of participants in S-1 group, an alpha (type I error) of 2.5%, a beta (type II error) of 10%, and a diversity of 78%. Using the random-effects model Trial Sequential Analysis, the resulting cumulative test statistic (Z-score) did not cross the adjusted threshold for

statistical significance (Figure 4). The Trial Sequential Analysis-adjusted CI was 0.27 to 1.40.

Figure 4. Trial Sequential Analysis comparing gemcitabine plus S-1 versus S-1 alone on the outcome 'all-cause mortality'. The diversity-adjusted required information size (DARIS) of n = 2655 trial participants was calculated based upon a proportion of mortality of 70% of the trial participants in the S-1 group, a relative risk reduction of 20% in the gemcitabine + S-1 group, an alpha (type I error) of 2.5%, a beta (type II error) of 10%, and a diversity of 78%. The blue curve presents the cumulative meta-analysis Z-score, and the inward-sloping dotted red curves present the adjusted threshold for statistical significance according to the two-sided trial sequential monitoring boundaries. The Trial Sequential Analysis-adjusted CI was 0.27 to 1.40.
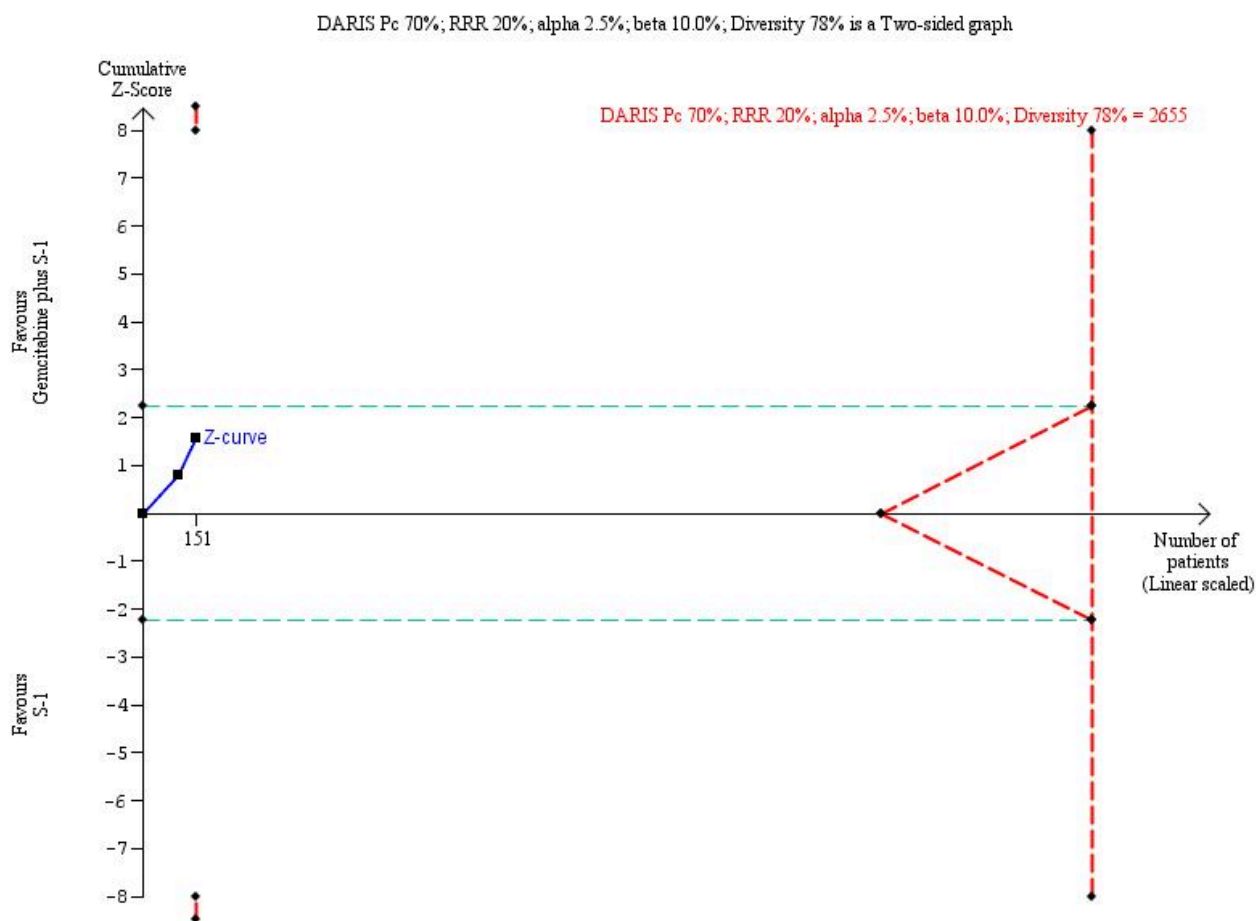
Health-related quality of life

There was no mention of health-related quality of life in any of the groups of this comparison.

Serious adverse events

This was covered only by the Morizane 2013 trial, in which two serious adverse events were reported in each group (gemcitabine/S-1 group and S-1 monotherapy group). Types of serious adverse events in this study included pneumonia, myocardial infarction, and hyponatraemia. The RR for the probability of serious adverse events was: 1.05 (95% CI 0.15 to 7.10; P = 0.96; participants = 90; Analysis 4.2), favouring neither gemcitabine nor non-gemcitabine regimens.

Time to progression of the tumour (reported as median time to progression)

There was no mention of time to progression of the tumour in any of the groups of this comparison.

Tumour response assessments

Tumour response was evaluated in accordance with the response evaluation in solid tumours criteria in this comparison. The RR for overall response rate (complete response and partial response) was 2.46 (95% CI 1.27 to 4.75; P = 0.007; I^2 = 0%; participants = 140; Analysis 4.3), favouring the gemcitabine-based regimen. The overall response rate was stratified according to tumour site only in the Morizane 2013 trial, in which the participants with gall bladder carcinomas achieved an overall response rate of 12.5% (2/16) in the gemcitabine plus S-1 group and 16.7% (3/18) in the S-1 alone group. The overall response rate for participants with non-gall bladder

carcinomas was 50% (14/28) in the gemcitabine plus S-1 group and 17.9% (5/28) in the S-1 alone group.

Non-serious adverse events

Non-serious adverse events were categorised in all included trials according to the National Cancer Institute common terminology criteria (NCI-CTC 2016), and we ranked them accordingly into grades one to four.

RR for all grades of anaemia (grade 1 - 4) was 1.26 (95% CI 1.00 to 1.59; P = 0.05; participants = 151; I^2 = 0%; Analysis 4.4), favouring neither gemcitabine nor non-gemcitabine regimens.

RR for high-grade anaemia (grade 3 - 4) was 2.94 (95% CI 0.62 to 13.89; P = 0.17; participants = 101; Analysis 4.5), favouring neither gemcitabine nor non-gemcitabine regimens.

RR for all grades of thrombocytopenia (grade 1 - 4) was 2.45 (95% CI 1.39 to 4.32 ; P = 0.002; I^2 = 0%; participants = 151; Analysis 4.6), favouring non-gemcitabine regimens.

RR for high-grade thrombocytopenia (grade 3 - 4) was 2.94 (95% CI 0.62 to 13.89; P = 0.17; participants = 101; Analysis 4.7), favouring neither gemcitabine nor non-gemcitabine regimens.

RR for all grades of neutropenia (grade 1 - 4) was 3.30 (95% CI 1.04 to 10.50 ; P = 0.04; I^2 = 66%; participants = 151; Analysis 4.8), favouring non-gemcitabine regimens.

RR for high-grade neutropenia (grade 3 - 4) was 15.20 (95% CI 3.84 to 60.14; P < 0.001; Analysis 4.9), favouring non-gemcitabine regimens.

RR for febrile neutropenia was 2.97 (95% CI 0.32 to 27.87; P = 0.34; I^2 = 0%; participants = 151; Analysis 4.10), favouring neither gemcitabine nor non-gemcitabine regimens.

5. Gemcitabine plus oxaliplatin versus best supportive care

One trial included data related to this comparison (Sharma 2010).

All-cause mortality

The RR for all-cause mortality at one year was 0.78 (95% CI 0.53 to 1.15; P = 0.20; participants = 40; Analysis 5.1), favouring neither gemcitabine nor non-gemcitabine-based chemotherapy. All-cause mortality was not stratified in this trial by tumour site, tumour stage, or performance status. The trial reports all-cause mortality at one year.

Health-related quality of life

There was no mention of health-related quality of life in any of the groups of this comparison.

Serious adverse events

There was no mention of serious adverse events in any of the groups of this comparison.

Time to progression of the tumour (reported as median time to progression)

There was no mention of time to progression of the tumour in any of the groups of this comparison.

Tumour response assessments

Tumour response was evaluated in accordance with the response evaluation in solid tumours criteria in this comparison. The RR for overall response rate (complete response and partial response) was

34.00 (95% CI 2.11 to 547.54; P = 0.01; participants = 40; Analysis 5.2), favouring the gemcitabine-based regimen.

Non-serious adverse events

There was no mention of non-serious adverse events in any of the groups of this comparison.

6. Gemcitabine plus oxaliplatin versus 5-fluorouracil plus folinic acid

One trial included data related to this comparison (Sharma 2010).

All-cause mortality

The RR for all-cause mortality at one year was 0.81 (95% CI 0.55 to 1.20 ; P = 0.29; participants = 41; Analysis 6.1), favouring neither gemcitabine nor non-gemcitabine regimens. All-cause mortality was not stratified in this trial by tumour site, tumour stage, or performance status. The trial reports all-cause mortality at one year.

Health-related quality of life

There was no mention of health-related quality of life in any of the groups of this comparison.

Serious adverse events

There was no mention of serious adverse events in any of the groups of this comparison.

Time to progression of the tumour (reported as median time to progression)

There was no mention of time to progression of the tumour in any of the groups of this comparison.

Tumour response assessments

Tumour response was evaluated in accordance with the response evaluation in solid tumours criteria in this comparison. The RR for overall response rate (complete response and partial response) was 2.15 (95% CI 0.64 to 7.29 ; P = 0.22; participants = 41; Analysis 6.2), favouring neither gemcitabine nor non-gemcitabine regimens.

Non-serious adverse events

There was no mention of non-serious adverse events in any of the groups of this comparison.

Following our protocol, we have also evaluated the harmful effects from Lee 2015, which is a retrospective study comparing gemcitabine plus cisplatin to capecitabine plus cisplatin. There were no cases of chemotherapy-related death or febrile neutropenia reported in this study. The most common haematologic grade 3 - 4 toxicity was neutropenia in both the gemcitabine and non-gemcitabine groups (15% and 14.4%, respectively). We have also evaluated the harmful effects from Raderer 1999, which is an observational non-randomised study evaluating 5-fluorouracil plus mitomycin C (cohort A) or gemcitabine monotherapy (cohort B). Haematologic adverse effects attributable to treatment were modest with both treatment regimens. Grade IV granulocytopenia was seen in 5% of the participants, severe thrombocytopenia occurred in 15% of the participants, and grade III anaemia was seen in 10% of 19 evaluable participants in cohort A. Among the 17 participants of cohort B

who were considered evaluable for toxicity, thrombocytopenia was the most commonly-observed haematologic side effect, with 12% of participants having grade III and 6% with grade IV thrombocytopenia. Only 6% had leukocytopenia grade II, and 6% had anaemia grade I.

7. Gemcitabine plus oxaliplatin versus 5-fluorouracil plus cisplatin plus radiotherapy

One trial included data related to this comparison (Phelip 2014).

All-cause mortality

The RR for all-cause mortality at one year was 0.56 (95% CI 0.21 to 1.52; P = 0.26; participants = 34; Analysis 7.1), favouring neither gemcitabine nor non-gemcitabine regimens.
All-cause mortality was not stratified in this trial by tumour site, tumour stage, or performance status. The trial reports all-cause mortality at one year.

Health-related quality of life

There was no mention of health-related quality of life in any of the groups of this comparison.

Serious adverse events

In Phelip 2014, eight participants suffered serious adverse events in the chemotherapy group versus six participants in the chemoradiotherapy group. The cause of serious adverse events was upper gastrointestinal bleeding in one case, with no mention of the details of hospitalisation of the other 13 participants. The RR for the probability of serious adverse events was 1.50 (95% CI 0.66 to 3.39; P = 0.33; participants = 34; Analysis 7.2), favouring neither gemcitabine nor non-gemcitabine regimens.

Time to progression of the tumour (reported as median time to progression)

There was no mention of time to progression of the tumour in any of the groups of this comparison.

Tumour response assessments

There was no mention of tumour response in any of the groups of this comparison.

Non-serious adverse events

Non-serious adverse events were categorised in all the included trials according to the National Cancer Institute common terminology criteria (NCI-CTC 2016), and we ranked them accordingly into grades one to four.
RR for high-grade neutropenia (grade 3 - 4) was 10.06 (95% CI 0.58 to 173.47; P = 0.11; participants = 34; Analysis 7.3), favouring neither gemcitabine nor non-gemcitabine regimens.

8. Gemcitabine plus mitomycin C versus capecitabine plus mitomycin C

One trial included data related to this comparison (Kornek 2004).

All-cause mortality

The RR for all-cause mortality at one year was 1.14 (95% CI 0.89 to 1.48 ; P = 0.30; participants = 51; Analysis 8.1), favouring neither gemcitabine nor non-gemcitabine regimens. All-cause mortality was not stratified in this trial by tumour site, tumour stage, or

performance status. The trial reports all-cause mortality at one year.

Health-related quality of life

There was no mention of health-related quality of life in any of the groups of this comparison.

Serious adverse events

There was no mention of serious adverse events in any of the groups of this comparison.

Time to progression of the tumour (reported as median time to progression)

There was no mention of time to progression of the tumour in any of the groups of this comparison.

Tumour response assessments

Tumour response was evaluated in this study in accordance with the World Health Organization criteria. The RR for overall response rate (complete response and partial response) was 0.65 (95% CI 0.25 to 1.72; P = 0.39; participants = 51; Analysis 8.2), favouring neither gemcitabine nor non-gemcitabine regimens. Overall response rate was not stratified in this trial by tumour site, tumour stage, or performance status.

Non-serious adverse events

Non-serious adverse events were categorised in all the included trials according to the National Cancer Institute common terminology criteria (NCI-CTC 2016), and we ranked them accordingly into grades one to four.
RR for all grades of thrombocytopenia (grade 1 - 4) was 0.56 (95% CI 0.29 to 1.06; P = 0.07; participants = 47; Analysis 8.3), favouring neither gemcitabine nor non-gemcitabine regimens.
RR for high-grade thrombocytopenia (grade 3 - 4) was 0.78 (95% CI 0.20 to 3.12; P = 0.73; participants = 47; Analysis 8.4), favouring neither gemcitabine nor non-gemcitabine regimens.

Summary of findings

Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; and Summary of findings 8 present our findings on the outcomes: all-cause mortality, serious adverse events, health-related quality of life, time to progression of the tumour, and non-serious adverse events. We downgraded the quality of the evidence by three levels because of within-study risk of bias due to high risk of bias; publication bias as it could not be assessed; and because of imprecision due to the small number of trials (only one trial or two trials contributing data). The certainty of the evidence of all the presented outcomes is therefore graded as very low.

DISCUSSION

Summary of main results

Based on the included trials, gemcitabine plus cisplatin combination may be associated with lower all-cause mortality compared with S-1 plus cisplatin combination. Gemcitabine plus vandetanib combination may be associated with higher response rates compared with vandetanib alone. Gemcitabine plus S-1 combination may be associated with higher response

rates compared with S-1 alone, and gemcitabine plus oxaliplatin may be associated with higher response rates compared with best supportive care. On the other hand, gemcitabine plus cisplatin combination may be associated with a higher risk of all grades and high-grade anaemia and thrombocytopenia. Similarly, gemcitabine plus S-1 combination may be associated with a higher risk of all grades of thrombocytopenia, all grades of neutropenia, and high-grade neutropenia. However, it has to be noted that the included trials were highly heterogeneous in their design, mixing single-agent chemo- or targeted therapy, radiochemotherapy, and supportive care. Thus, taking into consideration the overall low quality of data, we cannot draw definite conclusions. We note also that there were no properly-performed placebo-controlled studies in this review. This might have affected the assessment of intervention effects for all outcomes, with the possible exception of mortality.

We await the results of three ongoing randomised trials to provide data for this intervention with or without additional treatments for advanced biliary tract carcinoma (NCT02591030; NCT01470443; NCT03044587).

Overall completeness and applicability of evidence

The search strategy for randomised clinical trials was very wide, and additionally, by searching the reference lists of the included trials and by checking recent review articles, we made sure that we covered all relevant trials. However, we note that not all of the included trials provided data on all the primary outcomes of interest in this review; moreover, the control regimens are quite variable, which limits the applicability of the evidence. We have not searched the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), or the World Health Organiztion (WHO) clinical registry, and we did not contact pharmaceutical companies for unpublished trials. By focusing mainly on randomised clinical trials and not searching for observational studies reporting adverse events, we are well aware that we bias the review towards focusing more on potential benefits than on potential harms.

Quality of the evidence

The body of collected evidence does not allow a robust conclusion regarding the objectives of the review. We assessed the overall quality of the evidence as being of very low certainty, using the GRADE approach (GRADEpro 2008; Balshem 2011). This is because of the high risk of bias, small number of trials (imprecision), as well as marked heterogeneity (inconsistency). Details of the risk of bias assessment of included trials were as follows: there was a low risk of reporting bias in all trials except for Phelip 2014, and a low risk of attrition bias in all the included trials except for Li 2016. There was a low risk of performance bias in Santoro 2015; unclear risk in Kornek 2004 trial; and a high risk in Sharma 2010; Kang 2012; Morizane 2013; Phelip 2014 and Li 2016. There was a low risk of detection bias in Santoro 2015 trial; unclear risk in Kornek 2004; Kang 2012; and Phelip 2014 trials; and a high risk of detection bias in Morizane 2013 and Li 2016 trials. Detection bias (including allocation sequence generation and allocation concealment) was clearly reported by four trials (Kornek 2004; Morizane 2013; Santoro 2015; Li 2016); while it was unclearly reported by three trials (Sharma 2010; Kang 2012; Phelip 2014).

Potential biases in the review process

Publication bias might be an issue here; however, due to the fact that there were only one or two trials for each comparison, we were not able to assess this formally.

Agreements and disagreements with other studies or reviews

A meta-analysis of individual patient data combining the UK ABC-02 study (Valle 2010) and the Japanese BT22 study (Okusaka 2010) has been published (Valle 2014). However, the main research question of this meta-analysis was whether or not gemcitabine plus cisplatin combination is better than gemcitabine monotherapy.

Another meta-analysis has evaluated the efficacy and safety of gemcitabine-based chemotherapies in biliary tract cancer (Liu 2014), and included seven randomised trials (Kornek 2004; Okusaka 2010; Sharma 2010; Valle 2010; Kang 2012; Morizane 2013; Sasaki 2013); the conclusions indicated that gemcitabine-based combination chemotherapy is a potential first-line treatment for advanced biliary tract cancer, based on improved survival, albeit with additional toxicity.

AUTHORS' CONCLUSIONS

Implications for practice

In adults with advanced biliary tract carcinomas, the effects of gemcitabine or gemcitabine-based chemotherapy are uncertain on mortality and on overall response, compared with a range of inactive or active controls. The very low certainty of evidence is due to risks of bias, lack of information in the analyses and hence large imprecision, and possible publication bias. The confidence intervals exclude neither meaningful benefits nor lack of effect 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).

Implications for research

There is a need for large, high-quality randomised clinical trials of gemcitabine- and non-gemcitabine-based systemic therapy regimens for people with advanced biliary tract carcinomas. It is also important that the randomisation process is clearly described, as well as the interventions. The participant flow and data handling should be well specified. The trials must be designed and described following the SPIRIT statement (Standard Protocol Items: Recommendations for Interventional Trials; www.spirit-statement.org/) and the CONSORT statement (Consolidated Standards of Reporting Trials: www.consort-statement.org).

There is also a particular need for properly-conducted placebo-controlled randomised clinical trials, in order to provide better assessment of clinically-important outcomes.

ACKNOWLEDGEMENTS

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Disclaimer: The views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the Danish State or The Copenhagen Trial Unit.

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Sign-off editor: Christian Gluud, Denmark

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C H A R A C T E R I S T I C S O F S T U D I E S

Characteristics of included studies *[ordered by study ID]*

Kang 2012

Methods	The investigators conducted a single-centre randomised parallel-group phase II trial of S-1 plus cisplatin versus gemcitabine plus cisplatin as first-line therapy in people with advanced biliary tract carcinoma.
Participants	The study population consisted of people who had advanced biliary tract carcinoma not amenable to potentially curative surgery or definitive chemoradiotherapy and who had never received systemic chemotherapy. 96 participants were enrolled from March 2008 to March 2009. Male/female ratio: 62/34 Median age: 59 years
Interventions	49 participants were randomised to the cisplatin (60 mg/m^2 IV on day 1) and gemcitabine (1000 mg/m^2 IV at 10 mg/m^2/min) on days 1 and 8 every 3 weeks) group; 47 to cisplatin (60 mg/m^2 IV on day 1) plus S-1 (40 mg/m$^{2)}$ twice a day orally on days 1 – 14)
Outcomes	Progression-free survival, response rate, overall survival, and toxicity
Notes	Country of study: South Korea We contacted the authors for further details on 25 January 2016 but received no reply. Funding: this trial was supported by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health, Welfare and Family Affairs, Republic of Korea. (Grant Number: A070001).

Risk of bias

Bias	Authors' judgement	Support for judgement

Kang 2012 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Trial participants were randomly assigned to 1 of the 2 groups. However, the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not stated in the publication.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The following quote is from the original paper: "The present trial was an open-label, single-center, randomised phase II study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Statistical methods were clearly described and all participants were included in the analyses.
Selective reporting (reporting bias)	Low risk	All-cause mortality, tumour response, and adverse events were reported. It is to be noted, however, that the trial protocol was registered after the study started.
For-profit bias	Low risk	No evidence of industry sponsorship. The following quote is from the original paper: "This study was supported by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health, Welfare and Family Affairs, Republic of Korea. (Grant Number: A070001)"
Other bias	Unclear risk	Unclear risk of other biases

Kornek 2004

Methods	The phase II randomised parallel-group controlled trial aimed to investigate the therapeutic efficacy and tolerance of mitomycin C in combination with gemcitabine or capecitabine in previously untreated people with non-resectable metastatic biliary tract cancer. The exact time of recruitment of participants was not stated in the published report of the trial.
Participants	51 trial participants eligible for the study had, histologically or cytologically ascertained, non-resectable metastatic adenocarcinoma of the biliary tract. Male/female: 18/33 Median age: 66 years
Interventions	Group A (25 participants): mitomycin C 8 mg/m^2 on day 1 in combination with gemcitabine 2000 mg/m^2 on days 1 and 15 every 4 weeks; Group B (26 participants): mitomycin C 8 mg/m^2 on day 1 plus capecitabine 2000 mg/m^2/day on days 1–14, every 4 weeks. In both groups, chemotherapy was administered for 6 months unless progressive disease occurred earlier.
Outcomes	Progression-free survival, response rate, overall survival, and treatment tolerance.
Notes	Country of the study: Austria We contacted the authors for further details on 25 January 2016 but received no reply.

Kornek 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Trial participants were randomly assigned to 1 of the 2 groups and allocation was done though a central unit. The following is a quote from the original paper: "Patients were then assigned to one treatment regimen by the central office located at the University of Vienna."
Allocation concealment (selection bias)	Low risk	Allocation concealment was done by a central unit.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Trial participants were then assigned to 1 treatment regimen by the central office located at the University of Vienna. However, it is not clear whether the participants and personnel were blinded or not.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial participants were then assigned to 1 treatment regimen by the central office located at the University of Vienna. However, it is not clear whether the outcome assessors were blinded or not.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors clearly described their analyses (ITT) and included information about losses to follow-up/withdrawals.
Selective reporting (reporting bias)	Low risk	All-cause mortality, tumour response, and adverse events were reported.
For-profit bias	Unclear risk	We found no evidence on how the trial was funded.
Other bias	Unclear risk	Unclear risk of other biases

Li 2016

Methods	This randomised open-label clinical trial aimed to evaluate the efficacy and safety of the gemcitabine plus S-1 (GEM-S-1) combination for treating unresectable hilar cholangiocarcinoma. The trial was conducted between February 2009 to November 2012.
Participants	79 participants with unresectable hilar cholangiocarcinoma were randomised to the study groups. Male/female: 54/21 Mean age: 56.3 ± 7.83
Interventions	79 participants were allocated into 3 study groups (gemcitabine group, S-1 group, and gemcitabine+S-1 group respectively). Four participants discontinued the treatment because of financial hardship or unwillingness to continue the treatment because of advanced disease, and 75 participants out of 79 completed the study and were analysed (25 participants in each of the three arms).
Outcomes	1-year overall survival, progression-free survival, response rate, toxicity and side effects
Notes	For data analysis purposes, the gemcitabine plus S-1 group were considered as the intervention group, and outcomes from this group were compared against the S-1 monotherapy (i.e. non-gemcitabine-containing comparator) group.

Li 2016 *(Continued)*

Country of the study: China

We contacted the authors for further details on 4 July 2017 but received no reply.

Funding: this trial was supported in part by the National Natural Science Foundations of China (81170721) and Shanghai Pujiang Program (14PJ1407300).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Trial participants were randomly assigned to 1 of the 3 groups, as quoted from the original paper: "Eligible patients were randomly assigned to the gemcitabine/S-1, gemcitabine and S-1 groups via a computer-generated randomisation list."
Allocation concealment (selection bias)	Low risk	The following quote is from the original paper: "To conceal individual patient group assignments, a trial/data manager who was not involved in patient recruitment generated the patient random allocation sequence via computer."
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was an open-label clinical trial.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was an open-label clinical trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	The following quote is from the original paper: "79 patients were randomly allocated to the study groups. However, four patients discontinued the treatment because of financial hardship or the unwillingness to continue the treatment because of advanced disease", "Seventy-five out of 79 patients (94.9%) completed the analysis, with 25 subjects in each treatment group (gemcitabine, S-1, and gemcitabine-S-1)". There were no available outcome data about these remaining 4 patients.
Selective reporting (reporting bias)	Low risk	Although the study protocol cannot be accessed, the authors reported primary (OS and PFS) and secondary (objective RR and safety of chemotherapeutic agents) outcomes in the published results.
For-profit bias	Low risk	No evidence of industry sponsorship. The following quote is from the original paper: "This study was supported in part by the National Natural Science Foundations of China (81170721) and Shanghai Pujiang Program (14PJ1407300)"
Other bias	Unclear risk	Unclear risk of other bias

Morizane 2013

Methods	Phase II randomised parallel-group controlled trial; to evaluate the safety and efficacy of 2 regimens (S-1 alone or S-1 with gemcitabine) in the management of advanced biliary tract cancers
Participants	From February 2009 to April 2010, 101 trial participants were enrolled with unresectable or recurrent disease; histologically-proven adenocarcinoma or adenosquamous carcinoma in people with extrahepatic biliary duct, gall bladder or intrahepatic biliary duct carcinomas

Morizane 2013 *(Continued)*

	Male/female: 55/46
	Median age: 64 years
Interventions	Gemcitabine plus S-1 (gemcitabine: 1000 mg/m^2, day 1 and day 8; S-1: 60 mg/m^2, twice daily on days 1 - 14, repeated every 3 weeks) (51 participants); S-1 (80 mg/m^2, days 1 - 28, given orally twice daily for 4 weeks, followed by a 2-week rest, repeated every 6 weeks) (50 participants).
Outcomes	Progression-free survival, overall survival, response rate in participants with measurable lesions, the incidence of adverse events, and of serious adverse events
Notes	Country of the study: Japan We contacted the authors for further details 25 January 2016 but received no reply. Funding: the sponsor of the study was the Ministry of Health, Labour and Welfare, Japan, which had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Trial participants were randomly allocated to either the gemcitabine/S-1 or S-1 treatment groups, using a minimisation method with an algorithm (concealed from the investigator) to balance the following stratification factors: institution; primary site (gall bladder, others); and clinical stage (II, III, IV or recurrent). The following quote is from the original paper: "The data managers checked the eligibility, completed registration if appropriate, and randomly allocated the patient to either the GS or S-1 treatment group, using a minimization method with an algorithm (concealed to the investigator)"
Allocation concealment (selection bias)	Low risk	Trial participants were randomly allocated to either the gemcitabine/S-1 or S-1 treatment groups, using a minimisation method with an algorithm (concealed from the investigator) to balance the following stratification factors: institution; primary site (gall bladder, others); and clinical stage (II, III, IV or recurrent). The following quote is from the original paper: "The data managers checked the eligibility, completed registration if appropriate, and randomly allocated the patient to either the GS or S-1 treatment group, using a minimization method with an algorithm (concealed to the investigator)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	The following quote is from the original paper: "The treatment allocation was not masked from the investigators or the patients"
Blinding of outcome assessment (detection bias) All outcomes	High risk	The following quote is from the original paper: "The treatment allocation was not masked from the investigators or the patients"
Incomplete outcome data (attrition bias) All outcomes	Low risk	The follow-up and statistical methods were clearly described and all participants were included in the analyses.
Selective reporting (reporting bias)	Low risk	The study authors stated that "This study was registered at the UMIN Clinical Trials registry UMIN 000001685 (http://www.umin.ac.jp/ctr/index.htm)", but

Morizane 2013 *(Continued)*

		we could not access the protocol. All-cause mortality, tumour response, and adverse events were reported.
For-profit bias	Low risk	No evidence of industry sponsorship. The following quote is from the original paper: "The sponsor of the study was the Ministry of Health, Labour and Welfare, Japan, which had no role in the study design, data collection, data analysis, data interpretation, or writing of the report"
Other bias	Unclear risk	Unclear risk of other biases

Phelip 2014

Methods	An open-label, multicentre, randomised, parallel-group, 2-group controlled phase II trial
Participants	Between July 2006 and December 2010, 34 people with locally-advanced biliary tract cancers were included in 12 centres (18 in the chemoradiotherapy and 16 in the chemotherapy group). Male/female ratio: not reported Median age: not reported
Interventions	Chemoradiotherapy (fluorouracil infusion and cisplatin were given in association with radiotherapy (50 Gray)); Chemotherapy (gemcitabine + oxaliplatin for 6 months)
Outcomes	Progression-free survival, overall survival, toxicity, rate of biliary complications, and duration of hospitalisation
Notes	Country of the study: France We contacted the authors for further details 25 January 2016 but received no reply. Funding: this work was supported by 'Programme Hospitalier de Recherche Clinique 2001' from the French National Institute of Cancer (INCA) and sponsored by Centre Georges Leclerc, Dijon. Lilly company supplied gemcitabine and Sanofi company supplied oxaliplatin.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not specified. The following quote is from the original paper: "eligible patients were randomised at the 'Federation Francophonie de Cancerologie Digestive (FFCD)' data centre"
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation was not described. The following quote is from the original paper: "eligible patients were randomised at the 'Federation Francophonie de Cancerologie Digestive (FFCD)' data centre"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Practically, participants and personnel must have known the allocation during treatment (either chemoradiotherapy or chemotherapy alone). The following quote is from the original paper: "This study was an open, multicentre, randomised controlled phase II trial"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described.

Phelip 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Figure 1 of the original paper contains a detailed account of all participants in the study.
Selective reporting (reporting bias)	High risk	Tumour response was not reported. The trial was registered after the start of the study at clinicaltrials.gov (NCT00304135).
For-profit bias	High risk	The following quotes are from the original paper: "This work was supported by 'Programme Hospitalier de Recherche Clinique 2001' from the French National Institute of Cancer (INCA) and sponsored by Centre Georges Leclerc, Dijon." "We thank Lilly for supplying gemcitabine and Sanofi for supplying oxaliplatin".
Other bias	Unclear risk	Unclear risk of other biases

Santoro 2015

Methods	This phase II multicentre parallel-group randomised controlled trial evaluated the efficacy and tolerability of vandetanib alone compared with vandetanib plus gemcitabine or gemcitabine plus placebo in people with advanced biliary tract carcinoma.
Participants	173 participants were recruited from October 2008 to September 2012 at 19 centres across Italy who were diagnosed with advanced biliary tract cancer (gallbladder cancer, cancer of the extrahepatic bile duct, intrahepatic cholangiocarcinoma or ampullary carcinoma) and not receiving prior chemotherapy. Male/female: 81/92 Median age: 63.6 years
Interventions	Among the 173 treated participants, 8 participants were excluded from the ITT because of missing post-baseline assessment. The remaining 165 participants were randomised in a 1:1:1 ratio to 3 treatment groups: vandetanib 300 mg monotherapy (56 participants); vandetanib 100 mg plus gemcitabine (57 participants); gemcitabine plus placebo (52 participants).
Outcomes	Progression-free survival, overall survival, response rate, disease control rate, duration of response, performance status and safety outcomes
Notes	For data analysis purposes, the (vandetanib plus gemcitabine) group and the (gemcitabine plus placebo) group were considered as the intervention group and outcomes from these 2 groups were compared against the vandetanib alone (i.e. non-gemcitabine-containing comparator) group. Country of the study: Italy We contacted the authors for further details 25 January 2016 but received no reply. Funding: AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The following 2 quotes are from the original paper "Randomisation was based on concealed treatment allocation using sequentially numbered opaque,

Santoro 2015 *(Continued)*

		sealed envelopes". "The actual treatment given to individual patients was determined by a computer-generated randomisation scheme"
Allocation concealment (selection bias)	Low risk	The following quote is from the original paper: "Randomisation was based on concealed treatment allocation using sequentially numbered opaque, sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The following quote is from the clinicaltrials.gov record of the study: "Double Blind (Participant, Investigator, Outcomes Assessor)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The following quote is from the clinicaltrials.gov record of the study: "Double Blind (Participant, Investigator, Outcomes Assessor)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was a flow chart, detailing the included participants and their progress through the study "Figure-1 of the original paper".
Selective reporting (reporting bias)	Unclear risk	According to clinicaltrials.gov record of the trial, there are data on overall survival which were collected but not analysed.
For-profit bias	High risk	High risk of bias because of industry sponsorship of the study (AstraZeneca) The following quote is from the original paper "This study was sponsored by AstraZeneca".
Other bias	Unclear risk	Unclear risk of other biases

Sharma 2010

Methods	Single-centre randomised parallel-group 3-groups trial
Participants	99 trial participants with cytologically-proven unresectable or metastatic adenocarcinoma of gallbladder were screened from June 2006 to October 2008. 81 participants were then randomised into one of the three treatment groups and received treatment. Male/female:15/84 Median age: 49 years
Interventions	Group A: best supportive care (27 participants); Group B: fluorouracil /folinic acid (FUFA) (28 participants); Group C: gemcitabine/oxaliplatin (26 participants), for a maximum of 6 cycles
Outcomes	Progression-free survival, response rate, overall survival, and toxicity patterns
Notes	For our analysis, we divided the intervention group into two equal halves and compared each half with a different comparator group. Country of the study: India We contacted the authors for further details 25 January 2016 but received no reply.

Risk of bias

Sharma 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial participants were randomly assigned to 1 of 3 groups, but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not stated in the publication.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The following quote is from the original paper: "This was a randomised, controlled, open-label, single-center study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was a flow chart, detailing the included participants, and showing that only one participant was lost to follow-up without therapy "Figure-1 of the original paper".
Selective reporting (reporting bias)	Low risk	The authors stated that: "Clinical Trials repository link available on JCO.org"; but we could not find the link. Otherwise, all-cause mortality, tumour response, and adverse events were reported.
For-profit bias	Unclear risk	It is not clear how the study was funded.
Other bias	Unclear risk	Unclear risk of other biases

ITT: intention- to treat;**IV**: intravenous

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chen 2015	Gemcitabine was used in both randomised groups of the trial
Lee 2012	Gemcitabine was used in both randomised groups of the trial
Lee 2015	This publication was a retrospective analysis of clinical data through reviewing medical records
Leone 2016	Gemcitabine was used in both randomised groups of the trial
Malka 2014	Gemcitabine was used in both randomised groups of the trial
Moehler 2014	Gemcitabine was used in both randomised groups of the trial
Okusaka 2010	Gemcitabine was used in both randomised groups of the trial
Raderer 1999	Although the experimental gemcitabine group belongs to a prospectively-performed phase II trial, the comparator cohort was retrospectively assigned
Sasaki 2013	Gemcitabine was used in both randomised groups of the trial
Valle 2009	Gemcitabine was used in both randomised groups of the trial

Study	Reason for exclusion
Valle 2010	Gemcitabine was used in both randomised groups of the trial
Valle 2015	Gemcitabine was used in both randomised groups of the trial
Wan 2014	Gemcitabine was used in both randomised groups of the trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT01470443

Trial name or title	Study of GEMOX (gemcitabine/oxaliplatin) versus XELOX (xeloda/oxaliplatin) in advanced biliary tract carcinoma
Methods	Randomised, multicentre, open-label, phase III study
Participants	People with histologically- or cytologically-confirmed adenocarcinoma of biliary tract (intrahepatic, extrahepatic cholangiocarcinoma, gall bladder cancer) but ampulla of Vater cancer is excluded.
Interventions	Group I: GEMOX Group II: oxaliplatin
Outcomes	Primary outcome measures: • progression-free survival Secondary outcome measures: • safety profile
Starting date	December 2011
Contact information	Ho Yeong Lim, Professor of Medicine, Sungkyunkwan University School of Medicine, Department of Hematology and Oncology, Samsung Medical Center Mi Yeon Kwon, RN, miyeon.kwon@samsung.com
Notes	Estimated enrolment: 240 participants

NCT02591030

Trial name or title	Safety and efficacy of modified folfirinox versus gemcis in bile duct tumours (AMEBICA)
Methods	Randomised phase II/III study
Participants	People with locally-advanced, unresectable and/or metastatic bile duct tumours
Interventions	Group I: gemcitabine/cisplatin Group II: oxaliplatin/Irinotecan/folinic acid/5-fluorouracil
Outcomes	Primary outcomes: • percentage of participants alive without radiological progression (Phase II) • overall survival (Phase III)

NCT02591030 *(Continued)*

Secondary outcomes:

- overall survival
- tumour response
- toxicity of the treatment assessed according to NCI-CTC v 4.0
- biliary complications
- quality of life (EORTC QLQ-C30)

Starting date	November 2015
Contact information	Jean-Marc Phelip, PhD (0)477828320 ext +33 j.marc.phelip@chu-st-etienne.fr
	Lila GABA-BERKOUK (0)380393483 ext +33
	lila.gaba@u-bourgogne.fr
Notes	Estimated enrolment: 316 participants

NCT03044587
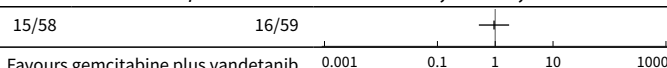
Trial name or title	Nal-IRI with 5-fluorouracil (5-FU) and leucovorin or gemcitabine plus cisplatin in advanced biliary-tract cancer (NIFE)
Methods	An open-label, non-comparative, randomised, multicentre phase II trial
Participants	People with:
	adenocarcinoma metastatic biliary tract cancer;
	adenocarcinoma of the biliary tract;
	adenocarinoma locally-advanced, non-resectable hepatocellular carcinoma;
	intrahepatic bile duct carcinoma;
	extrahepatic bile duct carcinoma.
Interventions	Group A: Na I-IRI + 5-FU + leucovorin
	Group B: cisplatin + gemcitabine
Outcomes	Primary outcome measures:
	• progression-free survival
	Secondary outcome measures:
	• 3-year overall survival
	• objective tumour response rate (ORR)
	• toxicity/safety
	• health-related quality of life EORTC QLQ-BIL21
Starting date	January 2017. This study is not yet open for participant recruitment.
Contact information	Dr Thomas J. Ettrich, Klinik für Innere Medizin I, Universitätsklinikum Ulm
Notes	Estimated enrolment: 92 participants

DATA AND ANALYSES

Comparison 1.   Gemcitabine plus vandetanib versus vandetanib alone

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Overall response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Grade 1 - 4 anaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Grade 3 - 4 anaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Grade 1 - 4 neutropenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Grade 3 - 4 neutropenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1.   Comparison 1 Gemcitabine plus vandetanib versus vandetanib alone, Outcome 1 Serious adverse events.

Study or subgroup	Gemcitabine plus vandetanib n/N	Vandetanib n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Santoro 2015	15/58	16/59		0.95[0.52,1.74]

Favours gemcitabine plus vandetanib   0.001   0.1   1   10   1000   Favours vandetanib

Analysis 1.2.   Comparison 1 Gemcitabine plus vandetanib versus vandetanib alone, Outcome 2 Overall response rate.

Study or subgroup	Gemcitabine plus vandetanib n/N	Vandetanib n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Santoro 2015	11/57	2/56		5.4[1.25,23.29]

Favours vandetanib   0.002   0.1   1   10   500   Favours gemcitabine plus vandetanib

Analysis 1.3.   Comparison 1 Gemcitabine plus vandetanib versus vandetanib alone, Outcome 3 Grade 1 - 4 anaemia.

Study or subgroup	Gemcitabine plus vandetanib n/N	Vandetanib n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Santoro 2015	7/58	1/59		7.12[0.9,56.08]

Favours gemcitabine plus vandetanib   0.01   0.1   1   10   100   Favours vandetanib

Analysis 1.4. Comparison 1 Gemcitabine plus vandetanib versus vandetanib alone, Outcome 4 Grade 3 - 4 anaemia.

Study or subgroup	Gemcitabine plus vandetanib		Vandetanib		Risk Ratio					Risk Ratio
	n/N		n/N		M-H, Random, 95% CI					M-H, Random, 95% CI
Santoro 2015	1/58		0/59							3.05[0.13,73.39]
			Favours gemcitabine plus vandetanib		0.002	0.1	1	10	500	Favours vandetanib

Analysis 1.5. Comparison 1 Gemcitabine plus vandetanib versus vandetanib alone, Outcome 5 Grade 1 - 4 neutropenia.

Study or subgroup	Gemcitabine plus vandetanib		Vandetanib		Risk Ratio					Risk Ratio
	n/N		n/N		M-H, Random, 95% CI					M-H, Random, 95% CI
Santoro 2015	7/58		0/59							15.25[0.89,261.11]
			Favours gemcitabine plus vandetanib		0.005	0.1	1	10	200	Favours vandetanib

Analysis 1.6. Comparison 1 Gemcitabine plus vandetanib versus vandetanib alone, Outcome 6 Grade 3 - 4 neutropenia.

Study or subgroup	Gemcitabine plus vandetanib		Vandetanib		Risk Ratio					Risk Ratio
	n/N		n/N		M-H, Random, 95% CI					M-H, Random, 95% CI
Santoro 2015	4/58		0/59							9.15[0.5,166.27]
			Favours gemcitabine plus vandetanib		0.005	0.1	1	10	200	Favours vandetanib
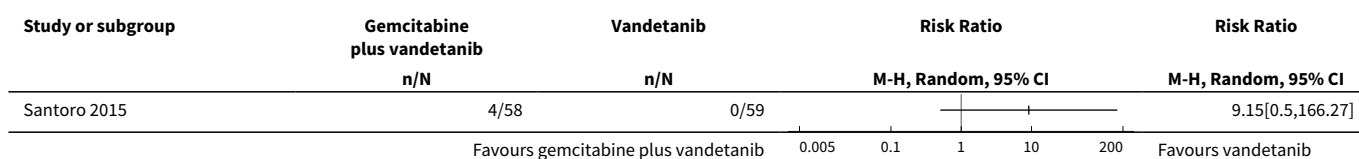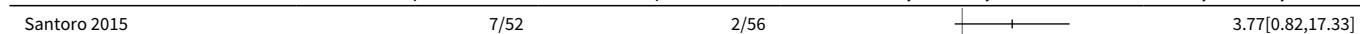
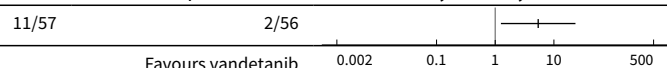## Comparison 2. Gemcitabine versus vandetanib

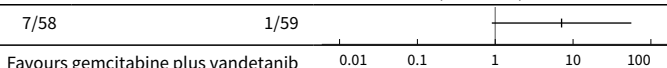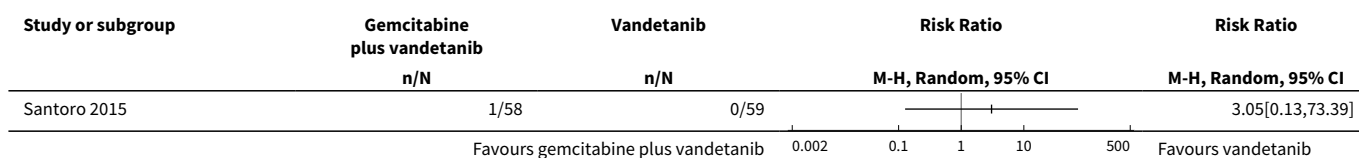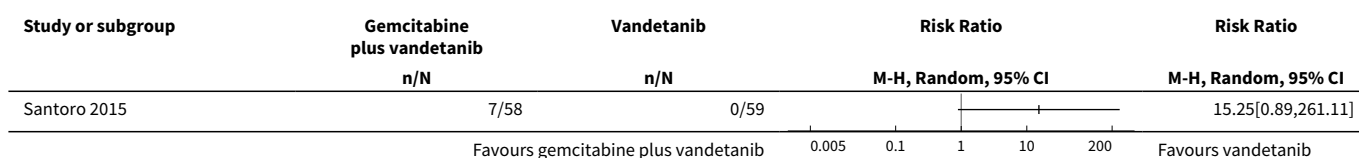| Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Overall response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Grade 1 - 4 anaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Grade 3 - 4 anaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Grade 1 - 4 neutropenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Grade 3 - 4 neutropenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Gemcitabine versus vandetanib, Outcome 1 Serious adverse events.

Study or subgroup	Gemcitabine n/N	Vandetanib n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Santoro 2015	12/56	16/59		0.79[0.41,1.52]

Favours gemcitabine 0.01 0.1 1 10 100 Favours vandetanib

Analysis 2.2. Comparison 2 Gemcitabine versus vandetanib, Outcome 2 Overall response rate.

Study or subgroup	Gemcitabine n/N	Vandetanib n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Santoro 2015	7/52	2/56		3.77[0.82,17.33]

Favours vandetanib 0.01 0.1 1 10 100 Favours gemcitabine

Analysis 2.3. Comparison 2 Gemcitabine versus vandetanib, Outcome 3 Grade 1 - 4 anaemia.

Study or subgroup	Gemcitabine n/N	Vandetanib n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Santoro 2015	7/56	1/59		7.38[0.94,58.05]

Favours gemcitabine 0.01 0.1 1 10 100 Favours vandetanib

Analysis 2.4. Comparison 2 Gemcitabine versus vandetanib, Outcome 4 Grade 3 - 4 anaemia.

Study or subgroup	Gemcitabine n/N	Vandetanib n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Santoro 2015	1/56	0/59		3.16[0.13,75.94]

Favours gemcitabine 0.01 0.1 1 10 100 Favours vandetanib

Analysis 2.5. Comparison 2 Gemcitabine versus vandetanib, Outcome 5 Grade 1 - 4 neutropenia.

Study or subgroup	Gemcitabine n/N	Vandetanib n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Santoro 2015	10/56	0/59		22.11[1.33,368.56]

Favours gemcitabine 0.002 0.1 1 10 500 Favours vandetanib
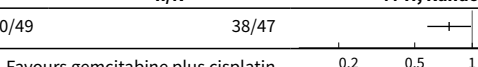
Analysis 2.6. Comparison 2 Gemcitabine versus vandetanib, Outcome 6 Grade 3 - 4 neutropenia.

Study or subgroup	Gemcitabine n/N	Vandetanib n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Santoro 2015	5/56	0/59		11.58[0.66,204.68]

Favours gemcitabine 0.005 0.1 1 10 200 Favours vandetanib

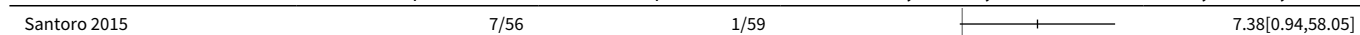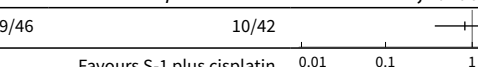## Comparison 3.   Gemcitabine plus cisplatin versus S-1 plus cisplatin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality at one year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Overall response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Grade 1 - 4 anaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Grade 3 - 4 anaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Grade 1 - 4 thrombocytopenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Grade 3 - 4 thrombocytopenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Grade 1 - 4 neutropenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Grade 3 - 4 neutropenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Febrile neutropenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 3.1.   Comparison 3 Gemcitabine plus cisplatin versus S-1 plus cisplatin, Outcome 1 All-cause mortality at one year.

Study or subgroup	Gemcitabine plus cisplatin n/N	S-1 plus cisplatin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kang 2012	30/49	38/47		0.76[0.58,0.98]

Favours gemcitabine plus cisplatin   0.2 0.5 1 2 5   Favours S-1 plus cisplatin

Analysis 3.2.   Comparison 3 Gemcitabine plus cisplatin versus S-1 plus cisplatin, Outcome 2 Overall response rate.

Study or subgroup	Gemcitabine plus cisplatin n/N	S-1 plus cisplatin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kang 2012	9/46	10/42		0.82[0.37,1.82]

Favours S-1 plus cisplatin   0.01 0.1 1 10 100   Favours gemcitabine plus cisplatin

Analysis 3.3. Comparison 3 Gemcitabine plus cisplatin versus S-1 plus cisplatin, Outcome 3 Grade 1 - 4 anaemia.

Study or subgroup	Gemcitabine plus cisplatin	S-1 plus cisplatin	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Kang 2012	47/49	4/47		11.27[4.41,28.83]
		Favours gemcitabine plus cisplatin	0.01 0.1 1 10 100	Favours S-1 plus cisplatin

Analysis 3.4. Comparison 3 Gemcitabine plus cisplatin versus S-1 plus cisplatin, Outcome 4 Grade 3 - 4 anaemia.

Study or subgroup	Gemcitabine plus cisplatin	S-1 plus cisplatin	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Kang 2012	11/49	1/47		10.55[1.42,78.56]
		Favours gemcitabine plus cisplatin	0.01 0.1 1 10 100	Favours S-1 plus cisplatin

Analysis 3.5. Comparison 3 Gemcitabine plus cisplatin versus S-1 plus cisplatin, Outcome 5 Grade 1 - 4 thrombocytopenia.

Study or subgroup	Gemcitabine plus cisplatin	S-1 plus cisplatin	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Kang 2012	28/49	4/47		6.71[2.55,17.68]
		Favours gemcitabine plus cisplatin	0.01 0.1 1 10 100	Favours S-1 plus cisplatin

Analysis 3.6. Comparison 3 Gemcitabine plus cisplatin versus S-1 plus cisplatin, Outcome 6 Grade 3 - 4 thrombocytopenia.

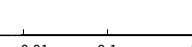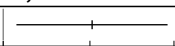| Study or subgroup	Gemcitabine plus cisplatin	S-1 plus cisplatin	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Kang 2012	11/49	2/47		5.28[1.23,22.55]
		Favours gemcitabine plus cisplatin	0.02 0.1 1 10 50	Favours S-1 plus cisplatin

Analysis 3.7. Comparison 3 Gemcitabine plus cisplatin versus S-1 plus cisplatin, Outcome 7 Grade 1 - 4 neutropenia.

Study or subgroup	Gemcitabine plus cisplatin	S-1 plus cisplatin	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Kang 2012	36/49	27/47		1.28[0.95,1.72]
		Favours gemcitabine plus cisplatin	0.2 0.5 1 2 5	Favour S-1 plus cisplatin

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Analysis 3.8. Comparison 3 Gemcitabine plus cisplatin versus S-1 plus cisplatin, Outcome 8 Grade 3 - 4 neutropenia.

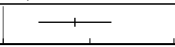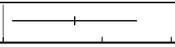| Study or subgroup	Gemcitabine plus cisplatin	S-1 plus cisplatin	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Kang 2012	24/49	14/47		1.64[0.97,2.78]
		Favours gemcitabine plus cisplatin	0.01 0.1 1 10 100	Favours S-1 plus cisplatin

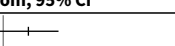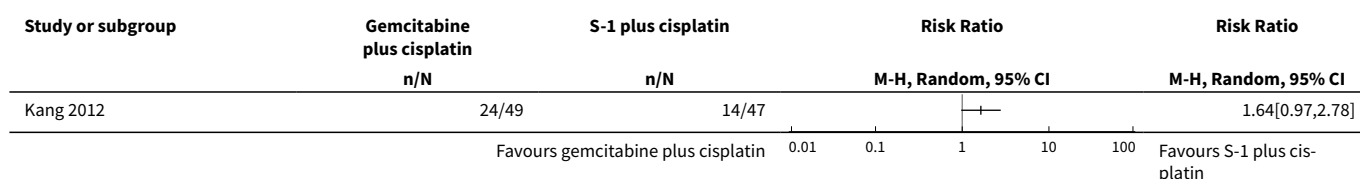## Analysis 3.9. Comparison 3 Gemcitabine plus cisplatin versus S-1 plus cisplatin, Outcome 9 Febrile neutropenia.

Study or subgroup	Gemcitabine plus cisplatin	S-1 plus cisplatin	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Kang 2012	2/49	0/47		4.8[0.24,97.42]
		Favours gemcitabine plus cisplatin	0.001 0.1 1 10 1000	Favours S-1 plus cisplatin
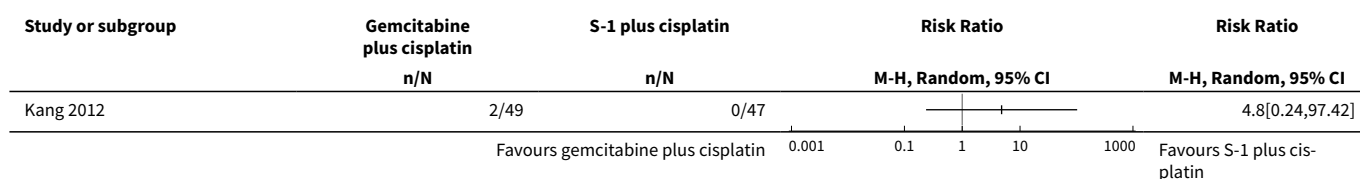
Comparison 4. Gemcitabine plus S-1 versus S-1

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality at one year	2	151	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.33, 1.13]
2 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Overall response rate	2	140	Risk Ratio (M-H, Random, 95% CI)	2.46 [1.27, 4.75]
4 Grade 1 - 4 anaemia	2	151	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.00, 1.59]
5 Grade 3 - 4 anaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Grade 1 - 4 thrombocytopenia	2	151	Risk Ratio (M-H, Random, 95% CI)	2.45 [1.39, 4.32]
7 Grade 3 - 4 thrombocytopenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Grade 1 - 4 neutropenia	2	151	Risk Ratio (M-H, Random, 95% CI)	3.30 [1.04, 10.50]
9 Grade 3 - 4 neutropenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Febrile neutropenia	2	151	Risk Ratio (M-H, Random, 95% CI)	2.97 [0.32, 27.87]

Analysis 4.1.   Comparison 4 Gemcitabine plus S-1 versus S-1, Outcome 1 All-cause mortality at one year.

Study or subgroup	Gemcitabine plus S-1	S-1	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Li 2016	10/25	23/25		46.26%	0.43[0.27,0.71]
Morizane 2013	25/51	30/50		53.74%	0.82[0.57,1.17]
Total (95% CI)	**76**	**75**		**100%**	**0.61[0.33,1.13]**
Total events: 35 (Gemcitabine plus S-1), 53 (S-1)					
Heterogeneity: Tau²=0.15; Chi²=4.1, df=1(P=0.04); I²=75.58%					
Test for overall effect: Z=1.57(P=0.12)					

Favours gemcitabine plus S-1 0.01 0.1 1 10 100 Favours S-1
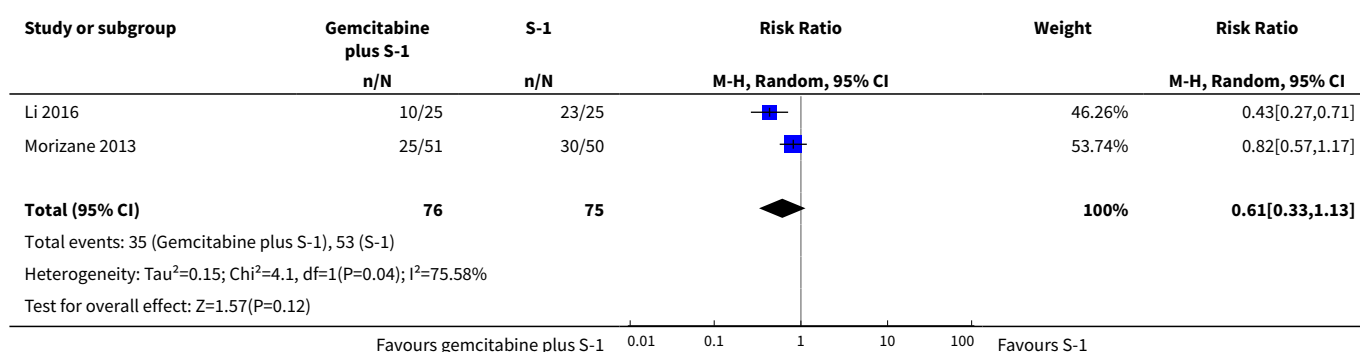
Analysis 4.2.   Comparison 4 Gemcitabine plus S-1 versus S-1, Outcome 2 Serious adverse events.

Study or subgroup	Gemcitabine plus S-1	S-1	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Morizane 2013	2/44	2/46		1.05[0.15,7.1]

Favours gemcitabine plus S-1 0.05 0.2 1 5 20 Favours S-1
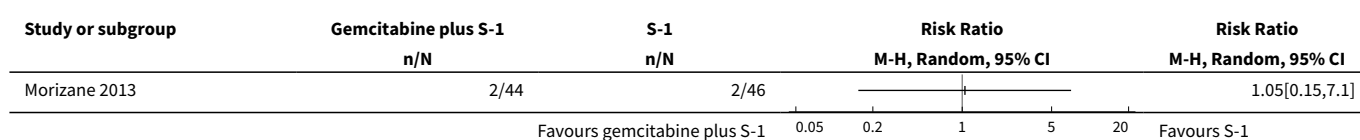
Analysis 4.3.   Comparison 4 Gemcitabine plus S-1 versus S-1, Outcome 3 Overall response rate.

Study or subgroup	Gemcitabine plus S-1	S-1	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Li 2016	9/25	2/25		21.22%	4.5[1.08,18.77]
Morizane 2013	16/44	8/46		78.78%	2.09[1,4.39]
Total (95% CI)	**69**	**71**		**100%**	**2.46[1.27,4.75]**
Total events: 25 (Gemcitabine plus S-1), 10 (S-1)					
Heterogeneity: Tau²=0; Chi²=0.89, df=1(P=0.34); I²=0%					
Test for overall effect: Z=2.68(P=0.01)					

Favours S-1 0.02 0.1 1 10 50 Favours gemcitabine plus S-1

Analysis 4.4.   Comparison 4 Gemcitabine plus S-1 versus S-1, Outcome 4 Grade 1 - 4 anaemia.

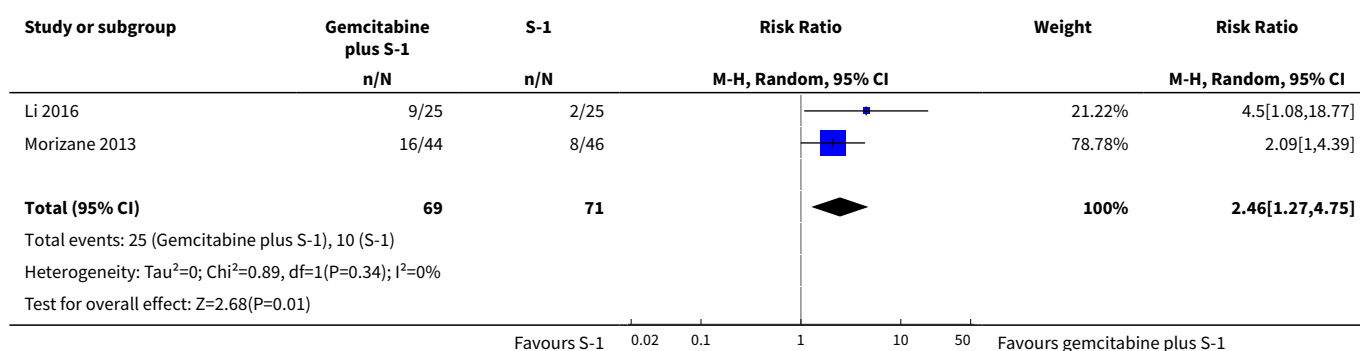| Study or subgroup	Gemcitabine plus S-1	S-1	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Li 2016	5/25	3/25		3.1%	1.67[0.45,6.24]
Morizane 2013	42/51	33/50		96.9%	1.25[0.99,1.58]
Total (95% CI)	**76**	**75**		**100%**	**1.26[1,1.59]**
Total events: 47 (Gemcitabine plus S-1), 36 (S-1)					
Heterogeneity: Tau²=0; Chi²=0.2, df=1(P=0.65); I²=0%					
Test for overall effect: Z=1.94(P=0.05)					

Favours gemcitabine plus S-1 0.1 0.2 0.5 1 2 5 10 Favours S-1

Analysis 4.5. Comparison 4 Gemcitabine plus S-1 versus S-1, Outcome 5 Grade 3 - 4 anaemia.

Study or subgroup	Gemcitabine plus S-1 n/N	S-1 n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Morizane 2013	6/51	2/50		2.94[0.62,13.89]

Favours gemcitabine plus S-1 0.01 0.1 1 10 100 Favours S-1
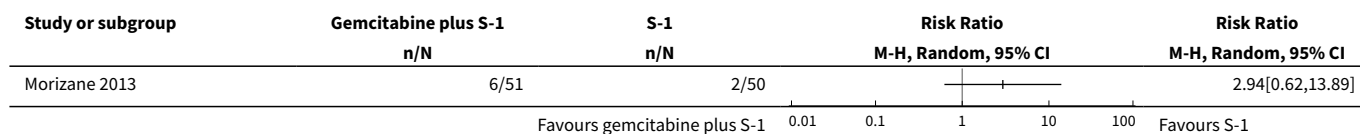
Analysis 4.6. Comparison 4 Gemcitabine plus S-1 versus S-1, Outcome 6 Grade 1 - 4 thrombocytopenia.

Study or subgroup	Gemcitabine plus S-1 n/N	S-1 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Li 2016	5/25	1/25		7.42%	5[0.63,39.79]
Morizane 2013	26/51	11/50		92.58%	2.32[1.29,4.17]
Total (95% CI)	**76**	**75**		**100%**	**2.45[1.39,4.32]**
Total events: 31 (Gemcitabine plus S-1), 12 (S-1)					
Heterogeneity: Tau²=0; Chi²=0.5, df=1(P=0.48); I²=0%					
Test for overall effect: Z=3.11(P=0)					

Favours gemcitabine plus S-1 0.01 0.1 1 10 100 Favours S-1
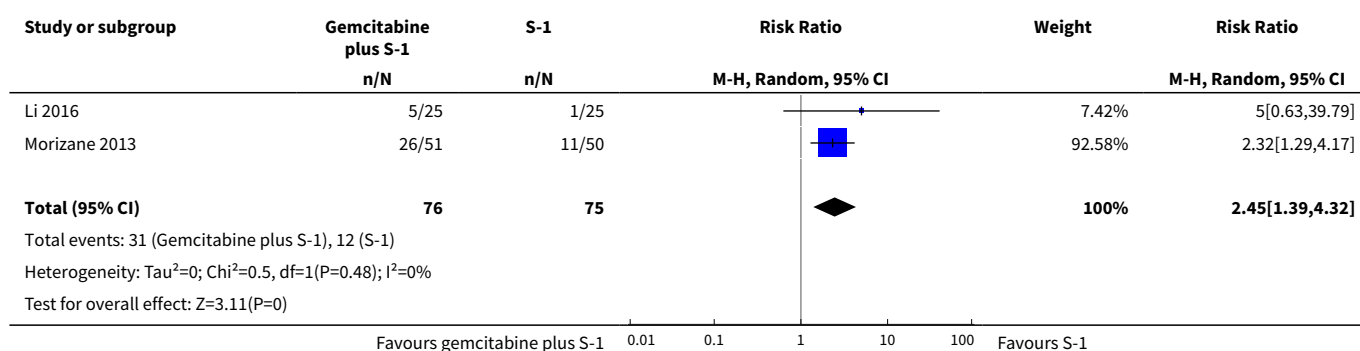
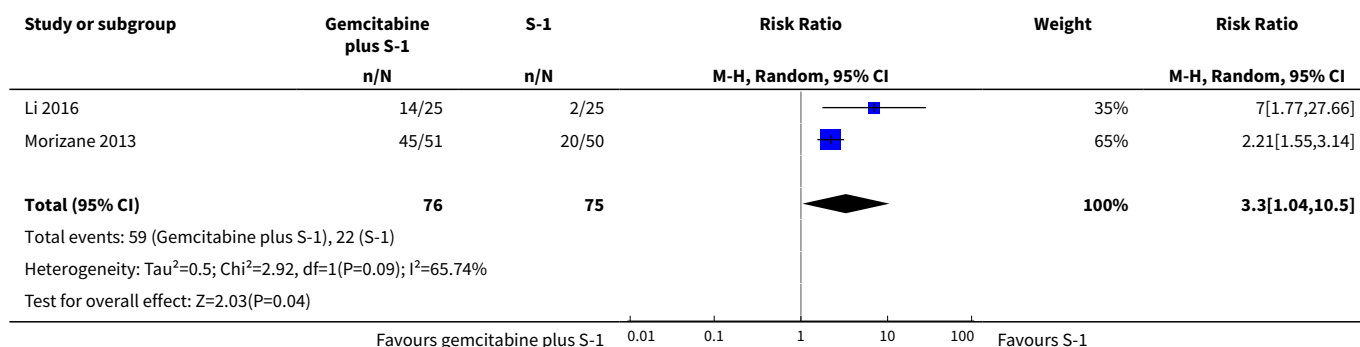## Analysis 4.7. Comparison 4 Gemcitabine plus S-1 versus S-1, Outcome 7 Grade 3 - 4 thrombocytopenia.

Study or subgroup	Gemcitabine plus S-1 n/N	S-1 n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Morizane 2013	6/51	2/50		2.94[0.62,13.89]

Favours gemcitabine plus S-1 0.01 0.1 1 10 100 Favours S-1
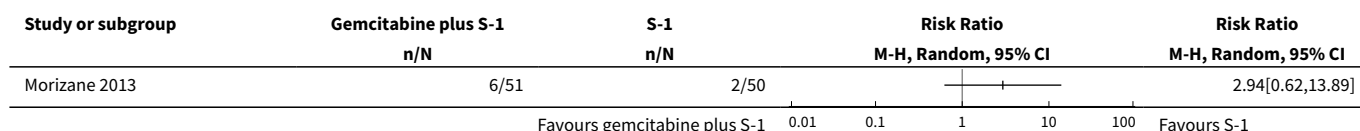
Analysis 4.8. Comparison 4 Gemcitabine plus S-1 versus S-1, Outcome 8 Grade 1 - 4 neutropenia.

Study or subgroup	Gemcitabine plus S-1 n/N	S-1 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Li 2016	14/25	2/25		35%	7[1.77,27.66]
Morizane 2013	45/51	20/50		65%	2.21[1.55,3.14]
Total (95% CI)	**76**	**75**		**100%**	**3.3[1.04,10.5]**
Total events: 59 (Gemcitabine plus S-1), 22 (S-1)					
Heterogeneity: Tau²=0.5; Chi²=2.92, df=1(P=0.09); I²=65.74%					
Test for overall effect: Z=2.03(P=0.04)					

Favours gemcitabine plus S-1 0.01 0.1 1 10 100 Favours S-1

Analysis 4.9. Comparison 4 Gemcitabine plus S-1 versus S-1, Outcome 9 Grade 3 - 4 neutropenia.

Study or subgroup	Gemcitabine plus S-1	S-1	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Morizane 2013	31/51	2/50		15.2[3.84,60.14]

Favours gemcitabine plus S-1 0.01 0.1 1 10 100 Favours S-1

Analysis 4.10. Comparison 4 Gemcitabine plus S-1 versus S-1, Outcome 10 Febrile neutropenia.

Study or subgroup	Gemcitabine plus S-1	S-1	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Li 2016	1/25	0/25		50.36%	3[0.13,70.3]
Morizane 2013	1/51	0/50		49.64%	2.94[0.12,70.56]
Total (95% CI)	**76**	**75**		**100%**	**2.97[0.32,27.87]**
Total events: 2 (Gemcitabine plus S-1), 0 (S-1)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.99); I²=0%					
Test for overall effect: Z=0.95(P=0.34)					

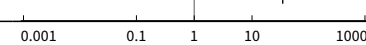Favours gemcitabine plus S-1 0.01 0.1 1 10 100 Favours S-1

Comparison 5. Gemcitabine plus oxaliplatin versus best supportive care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality at one year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Overall response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Gemcitabine plus oxaliplatin versus best supportive care, Outcome 1 All-cause mortality at one year.

Study or subgroup	Gemcitabine plus oxaliplatin	Best supportive care	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Sharma 2010	9/13	24/27		0.78[0.53,1.15]

Favours gemcitabine plus oxaliplatin 0.5 0.7 1 1.5 2 Favours best supportive care
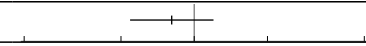
Analysis 5.2. Comparison 5 Gemcitabine plus oxaliplatin versus best supportive care, Outcome 2 Overall response rate.

Study or subgroup	Gemcitabine plus oxaliplatin	Best supportive care	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Sharma 2010	8/13	0/27		34[2.11,547.54]

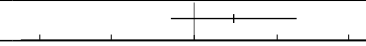Favours best supportive care 0.001 0.1 1 10 1000 Favours gemcitabine plus oxaliplatin

Comparison 6. Gemcitabine plus oxaliplatin versus fluorouracil plus folinic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality at one year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Overall response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6 Gemcitabine plus oxaliplatin versus fluorouracil plus folinic acid, Outcome 1 All-cause mortality at one year.

Study or subgroup	Gemcitabine plus oxaliplatin	Fluorouracil plus folinic	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Sharma 2010	9/13	24/28		0.81[0.55,1.2]

Favours gemcitabine plus oxaliplatin 0.2 0.5 1 2 5 Favours fluorouracil plus folinic

Analysis 6.2. Comparison 6 Gemcitabine plus oxaliplatin versus fluorouracil plus folinic acid, Outcome 2 Overall response rate.
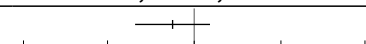
Study or subgroup	Gemcitabine plus oxaliplatin	Fluorouracil plus folinic	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Sharma 2010	4/13	4/28		2.15[0.64,7.29]

Favours fluorouracil plus folinic 0.05 0.2 1 5 20 Favours gemcitabine plus oxaliplatin

Comparison 7. Gemcitabine plus oxaliplatin versus 5-fluorouracil plus cisplatin plus radiotherapy
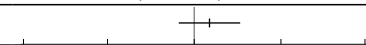
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality at one year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

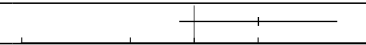| Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3 Grade 3 - 4 neutropenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7 Gemcitabine plus oxaliplatin versus 5-fluorouracil plus cisplatin plus radiotherapy, Outcome 1 All-cause mortality at one year.

Study or subgroup	Gemcitabine plus oxaliplatin	Fluorouracil plus cis-platin + radiotherapy	Risk Ratio		Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Phelip 2014	4/16	8/18			0.56[0.21,1.52]

Favours gemcitabine plus oxaliplatin 0.01 0.1 1 10 100 Favours fluorouracil plus cisplatin + radiotherapy

Analysis 7.2. Comparison 7 Gemcitabine plus oxaliplatin versus 5-fluorouracil plus cisplatin plus radiotherapy, Outcome 2 Serious adverse events.

Study or subgroup	Gemcitabine plus oxaliplatin	Fluorouracil plus cis-platin + radiotherapy	Risk Ratio		Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Phelip 2014	8/16	6/18			1.5[0.66,3.39]

Favours gemcitabine plus oxaliplatin 0.01 0.1 1 10 100 Favours fluorouracil plus cisplatin + radiotherapy

Analysis 7.3. Comparison 7 Gemcitabine plus oxaliplatin versus 5-fluorouracil plus cisplatin plus radiotherapy, Outcome 3 Grade 3 - 4 neutropenia.
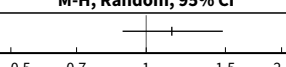
Study or subgroup	Gemcitabine plus oxaliplatin	Fluorouracil plus cis-platin + radiotherapy	Risk Ratio		Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Phelip 2014	4/16	0/18			10.06[0.58,173.47]

Favours gemcitabine plus oxaliplatin 0.002 0.1 1 10 500 Favours fluorouracil plus cisplatin + radiotherapy

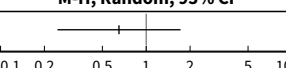## Comparison 8. Gemcitabine plus mitomycin C versus capecitabine plus mitomycin C

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 All-cause mortality at one year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Overall response rate	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Grade 1 - 4 thrombocytope-nia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

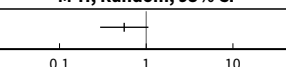| Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Grade 3 - 4 thrombocytopenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8 Gemcitabine plus mitomycin C versus capecitabine plus mitomycin C, Outcome 1 All-cause mortality at one year.

Study or subgroup	Gemcitabine plus mitomycin C n/N	Capecitabine plus mitomycin C n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kornek 2004	22/25	20/26		1.14[0.89,1.48]

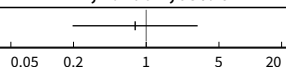Favours gemcitabine plus mitomycin C   0.5 0.7 1 1.5 2   Favours capecitabine plus mitomycin C

Analysis 8.2. Comparison 8 Gemcitabine plus mitomycin C versus capecitabine plus mitomycin C, Outcome 2 Overall response rate.

Study or subgroup	Gemcitabine plus mitomycin C n/N	Capecitabine plus mitomycin C n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kornek 2004	5/25	8/26		0.65[0.25,1.72]

Favours capecitabine plus mitomycin C   0.1 0.2 0.5 1 2 5 10   Favours gemcitabine plus mitomycin C

Analysis 8.3. Comparison 8 Gemcitabine plus mitomycin C versus capecitabine plus mitomycin C, Outcome 3 Grade 1 - 4 thrombocytopenia.

Study or subgroup	Gemcitabine plus mitomycin C n/N	Capecitabine plus mitomycin C n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kornek 2004	8/23	15/24		0.56[0.29,1.06]

Favours gemcitabine plus mitomycin C   0.01 0.1 1 10 100   Favours capecitabine plus mitomycin C

Analysis 8.4. Comparison 8 Gemcitabine plus mitomycin C versus capecitabine plus mitomycin C, Outcome 4 Grade 3 - 4 thrombocytopenia.

Study or subgroup	Gemcitabine plus mitomycin C n/N	Capecitabine plus mitomycin C n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kornek 2004	3/23	4/24		0.78[0.2,3.12]

Favours gemcitabine plus mitomycin C   0.05 0.2 1 5 20   Favours capecitabine plus mitomycin C

ADDITIONAL TABLES

Table 1. Explanations for Cochrane 'Summary of findings' tables

Examples from table	Explanation
Outcomes	The tables provide the findings for the most important outcomes for someone making a decision. These include potential benefits and harms, whether the included trials provide data for these outcomes or not. Additional findings may be reported elsewhere in the review.
Assumed control group risk	Assumed control group risks can be based either on the control group risks reported in the included trials or on epidemiological data from elsewhere. When only one control group risk is provided, it is normally the median control group risk across the trials that provided data for that outcome. Risk is the probability of an outcome occurring. The control group risk is the risk of an outcome occurring in the comparison group (without the intervention).
Corresponding intervention group risk	Risk is the probability of an outcome occurring. The intervention group risk is the risk of an outcome occurring in the group receiving the intervention.
Relative effect	**Relative effect or RR (risk ratio)** Relative effects are ratios. Here the relative effect is expressed as a risk ratio. Risk is the probability of an outcome occurring. An RR is the ratio between the risk in the intervention group and the risk in the control group. If the risk in the control group is 10% (100 per 1000) and the risk in the intervention group is 1% (10 per 1000), the RR is 10/100 or 0.10. If the RR is exactly 1.0, this means that there is no difference between the occurrence of the outcome in the intervention and the control group. It is unusual for the RR to be exactly 1.0, and understanding what it means if it is above or below this value depends on whether the outcome being counted is judged to be good or bad. If the RR is greater than 1.0, the intervention increases the risk of the outcome. If it is a good outcome (e.g. the birth of a healthy baby), an RR > 1.0 indicates a desirable effect for the intervention, whereas if the outcome is bad (e.g. death), an RR > 1.0 would indicate an undesirable effect. If the RR is less than 1.0, the intervention decreases the risk of the outcome. This indicates a desirable effect if it is a bad outcome (e.g. death) and an undesirable effect if it is a good outcome (e.g. birth of a healthy baby). **What is the difference between absolute and relative effects?** The effect of an intervention can be described by comparing the risk of the intervention group with the risk of the control group. Such a comparison can be made in different ways. One way to compare two risks is to calculate the difference between the risks. This is the absolute effect. Consider the risk for blindness in a person with diabetes over a five-year period. If the risk for blindness is found to be 20 in 1000 (2%) in a group of people treated conventionally and 10 in 1000 (1%) in people treated with a new drug, the absolute effect is derived by subtracting the intervention group risk from the control group risk: 2%/1% = 1%. Expressed in this way, it can be said that the new drug reduces the five-year risk for blindness by 1% (absolute effect is 10 fewer per 1000). Another way to compare risks is to calculate the ratio of the two risks. Given the data above, the relative effect is derived by dividing the two risks, with the intervention risk being divided by the control risk: 1% ÷ 2% = ½ (0.50). Expressed in this way, as the 'relative effect', the five-year risk for blindness with the new drug is 1/2 the risk with the conventional drug. Here the table presents risks as x per 1000 (or 100, etc.) instead of %, as this tends to be easier to understand. Whenever possible, the table presents the relative effect as the RR. Usually the absolute effect is different for groups that are at high and low risk, whereas the relative effect often is the same. Therefore, when it is relevant, we have reported indicative risks for groups at different levels of risk. Two or three indicative control group risks and the corresponding inter-

Table 1.   Explanations for Cochrane 'Summary of findings' tables *(Continued)*

	vention group risks are presented when there are important differences across different populations.
Mean difference	The mean difference (MD) is the average difference between the intervention group and the control group across trials. Here a weighted MD is used, which means the results of some of the trials make a greater contribution to the average than others. Trials with more precise estimates for their results (narrower confidence intervals) are given more weight.
	This way of measuring effect is used when combining or comparing data for continuous outcomes, such as weight, blood pressure, or pain measured on a scale. When different scales are used to measure the same outcome, e.g. different pain scales, a standardised mean difference (SMD) may be provided. This is a weighted mean difference standardised across trials giving the average difference in standard deviations for the measures of that outcome.
Confidence interval	A confidence interval (CI) is a range around an estimate that conveys how precise the estimate is; in this example the result is the estimate of the intervention group risk. The CI is a guide to how sure we can be about the quantity we are interested in (here the true absolute effect). The narrower the range between the two numbers, the more confident we can be about what the true value is; the wider the range, the less sure we can be. The width of the CI reflects the extent to which chance may be responsible for the observed estimate (with a wider interval reflecting more chance).
95% confidence interval	As explained above, the CI indicates the extent to which chance may be responsible for the observed numbers. In the simplest terms, a 95% CI means that we can be 95% confident that the true size of effect is between the lower and upper confidence limit (e.g. 0 and 3 in the blindness drugs example mentioned above). Conversely, there is a 5% chance that the true effect is outside of this range.
Not statistically significant	Statistically significant means that a result is unlikely to have occurred by chance. The usual threshold for this judgement is that the results, or more extreme results, would occur by chance with a probability of less than 0.05 if the null hypothesis (no effect) were true. When results are not statistically significant, as in this example, this is stated to alert users to the possibility that the results may have occurred by chance.
Number of participants (trials)	The table provides the total number of participants across trials and the number of trials that provided data for that outcome. This indicates how much evidence there is for the outcome.
Certainty of the evidence	The certainty of the evidence is a judgement about the extent to which we can be confident that the estimates of effect are correct. These judgements are made using the GRADE system, and are provided for each outcome. The judgements are based on the type of study design (randomised trials versus observational trials), the risk of bias, the consistency of the results across trials, and the precision of the overall estimate across trials.
	For each outcome, the certainty of the evidence is rated as high, moderate, low, or very low using the following definitions:
	• **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect • **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different • **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect • **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
-	A - indicates that the information is not relevant.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	June 2017	(gemcitabine) AND ((((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC) OR (bil* or cholangio*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*))
Cochrane Central Register of Controlled Trials Register (CENTRAL) in the Cochrane Library	2017, Issue 5	#1 gemcitabine
		#2 MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees
		#3 (((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC)
		#4 MeSH descriptor: [Biliary Tract Neoplasms] explode all trees
		#5 MeSH descriptor: [Cholangiocarcinoma] explode all trees
		#6 MeSH descriptor: [Adenoma, Bile Duct] explode all trees
		#7 (Bil* or cholangio*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)
		#8 #2 or #3 or #4 or #5 or #6 or #7
		#9 #1 and #8
MEDLINE Ovid	From 1946 to June 2017	1. gemcitabine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
		2. exp Carcinoma, Hepatocellular/
		3. (((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
		4. exp Biliary Tract Neoplasms/
		5. Cholangiocarcinoma/
		6. Adenoma, Bile Duct/
		7. ((Bil* or cholangio*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
		8. 2 or 3 or 4 or 5 or 6 or 7
		9. 1 and 8
		10. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

(Continued)

		11. 9 and 10
Embase Ovid	From 1974 to June 2017	1. exp gemcitabine/
		2. gemcitabine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
		3. 1 or 2
		4. exp liver cell carcinoma/
		5. (((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
		6. exp biliary tract tumor/
		7. exp bile duct carcinoma/
		8. ((Bil* or cholangio*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
		9. 4 or 5 or 6 or 7 or 8
		10. 3 and 9
		11. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
		12. 10 and 11
LILACS (Bireme)	From 1982 to June 2017	gemcitabine [Words] and ((((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom$ or cancer$ or neoplasm$ or malign$ or tumo$)) or HCC) OR (bil$ or cholangio$) and (carcinom$ or cancer$ or neoplasm$ or malign$ or tumo$)) [Words]
Science Citation Index Expanded (Web of Science)	From 1900 to June 2017	#7 #6 AND #5
		#6 TS=(random* or blind* or placebo* or meta-analys*)
		#5 #4 AND #1
		#4 #3 OR #2
		#3 TS=((Bil* or cholangio*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*))
		#2 TS=(((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC)
		#1 TS=(gemcitabine)
Conference Proceedings Citation Index – Science (Web of Science)	From 1990 to June 2017	#7 #6 AND #5
		#6 TS=(random* or blind* or placebo* or meta-analys*)
		#5 #4 AND #1
		#4 #3 OR #2

(Continued)

#3 TS=((Bil* or cholangio*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*))

#2 TS=(((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC)

#1 TS=(gemcitabine)

CONTRIBUTIONS OF AUTHORS

Omar Abdel-Rahman: writing and revising the review
Zeinab Elsayed: revising the review
Hesham El Halawani: writing and revising the review
All review authors agreed on the final version of the review.

DECLARATIONS OF INTEREST

Omar Abdel-Rahman: none known
Zeinab Elsayed: none known
Hesham El Halawani: none known

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Methods: Types of interventions

- We dropped the last two points mentioned in the protocol section Types of interventions, which was originally: " high-dose gemcitabine-based chemotherapy versus low-dose gemcitabine-based chemotherapy; one type of gemcitabine-based chemotherapy versus another gemcitabine-based chemotherapy", in order to comply with what we have written in the Types of studies section of the protocol, which reads: "All randomised clinical trials, irrespective of language or publication status, comparing intravenous administration of gemcitabine monotherapy or gemcitabine-based combination to other treatments (excluding gemcitabine) or to placebo or no intervention". Thus, we have not included any studies comparing two different gemcitabine-based regimens.

The Types of interventions now reads in the review as:

Intravenous gemcitabine (monotherapy or combination therapy) versus placebo or no treatment, or treatments other than gemcitabine

- gemcitabine-based chemotherapy versus placebo or no intervention;
- gemcitabine-based chemotherapy versus chemotherapy without gemcitabine.

Results

- We have introduced (post hoc) the common terminology criteria of adverse events (CTCAE 2010) in the assessment of non-serious adverse events, because this is the most widely accepted and standardised method of assessing toxicity to anticancer agents worldwide.

INDEX TERMS

Medical Subject Headings (MeSH)

Ampulla of Vater; Antimetabolites, Antineoplastic [adverse effects] [*therapeutic use]; Antineoplastic Combined Chemotherapy Protocols [adverse effects] [*therapeutic use]; Biliary Tract Neoplasms [*drug therapy] [mortality] [pathology]; Capecitabine [administration & dosage] [adverse effects]; Cholangiocarcinoma [*drug therapy] [mortality] [pathology]; Cisplatin [administration & dosage] [adverse effects]; Deoxycytidine [adverse effects] [*analogs & derivatives] [therapeutic use]; Drug Combinations; Gallbladder Neoplasms [drug therapy] [mortality] [pathology]; Mitomycin [administration & dosage] [adverse effects]; Organoplatinum

Compounds [administration & dosage] [adverse effects]; Oxaliplatin; Oxonic Acid [administration & dosage] [adverse effects]; Piperidines [administration & dosage] [adverse effects]; Quinazolines [administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Tegafur [administration & dosage] [adverse effects]

MeSH check words

Female; Humans; Male