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META-ANALYSIS

Efficacy and safety of gemcitabine-based chemotherapies in biliary tract cancer: A meta-analysis

Heng Liu, Qi-Di Zhang, Zheng-Hong Li, Qing-Qing Zhang, Lun-Gen Lu

Heng Liu, Qi-Di Zhang, Zheng-Hong Li, Qing-Qing Zhang, Lun-Gen Lu, Department of Gastroenterology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200080, China

Author contributions: Lu LG and Liu H designed the research; Liu H, Zhang QQ and Li ZH searched the databases, Liu H, Zhang QD and Lu LG performed the data extraction; Liu H analyzed the data; Liu H and Lu LG wrote the paper.

Correspondence to: Lun-Gen Lu, MD, Professor, Chief, Department of Gastroenterology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, No. 100 Haining Road, Hongkou District, Shanghai 200080, China. lungenlu1965@163.com

Telephone: +86-21-63240090 Fax: +86-21-63241377

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Abstract

AIM: To investigate the efficacy and safety of gemcitabine (Gem)-based combination chemotherapies for the treatment of advanced biliary tract cancer.

METHODS: Clinical trials were identified by searching scientific literature databases (PubMed, EMBASE and the Cochrane Library) for studies published between 1975 and 2013. Two reviewers independently evaluated the relevant studies and manually searched references from these reports to locate additional eligible studies. The disease response and control rates, progression-free and overall survivals, and the grade 3-4 toxicities were evaluated by a meta-analysis. Odds-ratios (ORs) of the disease response and control rates and grade 3-4 toxicities, and the mean difference (MD) of both progression-free and overall survivals were calculated and used for statistical analysis.

RESULTS: Seven randomized trials with a total of 858 patients were selected and included in the final analysis. The studies were divided into subgroups based on the chemotherapy regimens, including Gem-based and non-Gem-based chemotherapies. The overall analyses revealed that the patients treated with Gem-based combination chemotherapy had significantly higher disease response rates [OR = 1.69, 95% confidence interval (CI): 1.17-2.43; P = 0.01], a longer progression-free survival (MD = 1.95, 95%CI: 0.90-3.00; P = 0.00) and a longer overall survival (MD = 1.85, 95%CI: 0.26-3.44; P = 0.02). A higher incidence of grade 3-4 hematological toxicities, including leukopenia (OR = 2.98, 95%CI: 1.44-6.20; P = 0.00), anemia (OR = 2.96, 95%CI: 1.79-4.92; P = 0.00) and neutropenia (OR = 2.80, 95%CI: 1.39-5.64; P = 0.00) was found in the Gem-based combination chemotherapy group compared with the Gem monotherapy and non-Gem-based chemotherapy groups.

CONCLUSION: Gem-based combination chemotherapy is a potential first-line treatment for advanced biliary tract cancer as a result of improved survival, though with additional toxicity.

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Key words: Biliary tract cancer; Combination chemotherapy; Gemcitabine; Meta-analysis; Randomized trial

Core tip: To investigate the efficacy and safety of gemcitabine (Gem)-based combination chemotherapy for the treatment of advanced biliary tract cancer, the authors analyzed the potential impact of Gem-based combination chemotherapy and other regimens on the outcomes and toxicities of the patients using meta-analysis methodologies. Meta-analysis showed that compared with Gem monotherapy and non-Gem-based chemotherapy, Gem-based combination chemotherapy provided a modest improvement in survival but was associated with more toxicity.

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INTRODUCTION

Biliary tract cancer (BTC) refers to tumors that develop in the bile ducts and gall bladder and includes cholangiocarcinomas and gallbladder carcinomas[1]. BTC is a heterogeneous group of relatively rare tumors that account for about 3% of all gastrointestinal malignancies[1] and is the second most common cause of primary hepatic tumors[2]. Globally, hepatobiliary malignancies account for 13% of cancer-related deaths; 10%-20% of these deaths are attributable to BTC[3]. Epidemiologic studies have indicated that the incidence of BTC has increased rapidly worldwide in previous decades, particularly in Asian countries[1,4,5]. Despite advances in the diagnosis, staging and surgical management of BTC during the past decade, patients with BTC have a reported five-year survival rate that approaches only 15%[4] and an overall median survival of only 6.3 mo[6]. Surgical resection may be the only potentially curative therapeutic option. Unfortunately, due to the late clinical presentation, most BTC patients are diagnosed at an advanced stage when surgical resection is not feasible and treatment options are limited[5]. Hence, chemotherapeutic treatment is usually recommended for patients with unresectable advanced BTC or for patients who relapse subsequent to surgery[7].

Gemcitabine (Gem) emerged as a treatment for pancreatic cancer and has been explored as a treatment for advanced biliary cancer since 1998[8]. To improve the clinical efficacy, systemically administered Gem is often combined with a second cytotoxic agent, such as platinum analogs, fluoropyrimidine, or a targeted cytotoxic agent. The results from several phase Ⅱ studies suggest that Gem, alone or in combination with other agents, has been relatively effective for treating BTC[5,9]. However, most of these studies were small, single-arm and nonrandomized trials. Therefore, the role of Gem-based chemotherapy for patients with advanced BTC has not been clearly established. Until 2010, data from the largest randomized biliary tract trial to date indicated that the overall survival was significantly higher in the Gem and cisplatin arms *vs* the Gem single-agent treatment (11.7 mo *vs* 8.1 mo)[10]. Based on these results, Gem combined with cisplatin was established as the new standard of therapy for advanced, unresectable BTC[7]. Since that time, several randomized trials[11-14] comparing Gem-based combination chemotherapy with other regimens have been published. However, the results of these trials were conflicting, which has made the role of Gem-based combination chemotherapy controversial. Using these data, we conducted a meta-analysis to evaluate the efficacy and safety of Gem-based combination chemotherapy in advanced BTC treatment. The aim of this study was to assess whether Gem-based combination chemotherapy improves BTC prognosis compared with other treatment regimens.

MATERIALS AND METHODS

Search methods

PubMed, EMBASE and the Cochrane Library were systematically searched using the following combination of search terms: "biliary tract cancer", "gallbladder carcinoma", "cholangiocarcinoma" and "gemcitabine". The search was performed in August 2013 and updated in November 2013 to identify relevant publications between 1975 and 2013; there were no language restrictions. All potentially relevant studies were retrieved, and their references were evaluated to identify additional eligible studies.

Inclusion and exclusion criteria

Studies were eligible for inclusion in the meta-analysis if they met all of the following criteria: (1) advanced BTC patients (with unresectable or metastatic cancer); (2) Gem-based combination chemotherapy at any line; (3) reported disease response rate (DRR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and toxicities; and (4) structured as randomized controlled trials. Non-randomized trials and studies that repeated existing research were excluded to avoid clinical heterogeneity between studies.

Date extraction and quality assessment

Two independent reviewers (Liu H and Zhang QD) extracted the data from the eligible studies. A third reviewer (Lu LG) was consulted to resolve any disagreements. The following data were extracted from the included studies: first author's name, year of publication, number of patients enrolled in each treatment group, patient age (median and range), proportion of male participants, treatment regimens, numbers and rates of DRR, DCR, PFS, and OS and numbers and rates of each type of grade 3-4 toxicity.

Study quality was assessed with Jadad scores[15] using the following criteria: quality of randomization, quality of allocation concealment, quality of double-blinding, and quality of withdrawals and dropouts in the study description. The studies scored one point for each criterion met. Additional points were given for each of the following conditions that were met: randomization sequence method was described by computer or randomized number, method of allocation concealment was described and was appropriate, or a detailed description of proper double blinding methods was provided. Based on these criteria, high-quality studies scored a total of at least four points.

Statistical analysis

Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the DRR and the DCR using

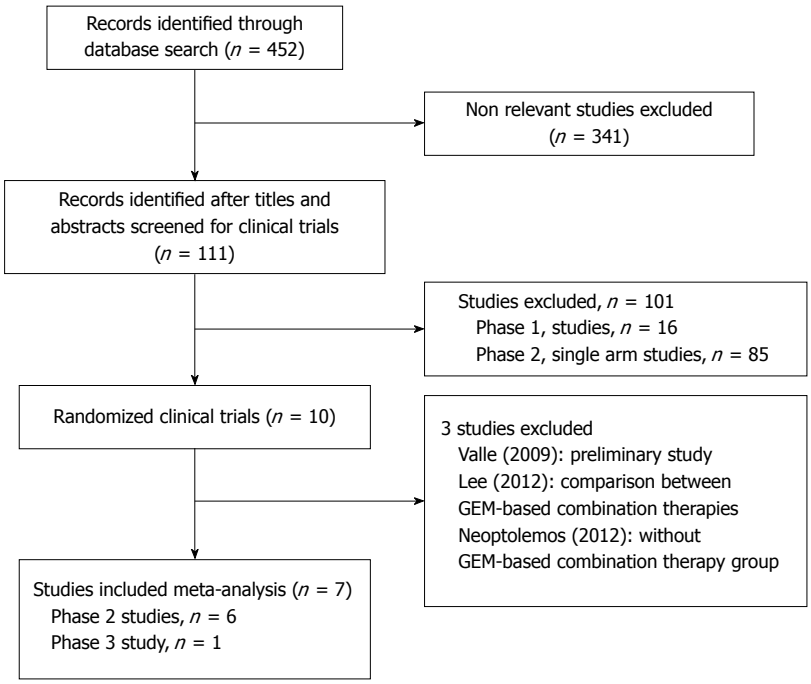


Figure 1 Flow diagram of the literature search and the study selection process. GEM: Gemcitabine.

Review Manger 5.2 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). The mean differences (MDs) with 95%CIs were calculated for the DRR and the DCR. Statistical heterogeneity among studies was assessed using Cochran's Q-test and the I^2 statistic[16]. A P value < 0.10 for the Q-test or an I^2 > 50% indicated study heterogeneity; in either case, a DerSimonian-Laird random effects model was used. Otherwise, a Mantel-Haenszel fixed effects method was used. If heterogeneity was found, a sensitivity analysis was performed to identify the potential sources of heterogeneity. Egger's and Begg's tests were used to measure potential publication bias. Statistical significance from two-sided analyses was indicated by a $P < 0.05$. Subgroup analyses were used to compare the efficacy and safety of gemcitabine-based combination chemotherapy with Gem monotherapy and non-Gem-based chemotherapy.

RESULTS

Literature search and selection flow

The study selection flow is depicted in Figure 1. Initially, 452 records were identified from PubMed, EMBASE and the Cochrane Library. After the initial review of the titles and abstracts, 111 relevant clinical trials were retrieved for detailed assessment, including ten randomized trials. As the scheme depicts, seven studies[10-14,17,18] met our inclusion criteria and were included in the quantitative synthesis, while the other three studies[19-21] were excluded.

Characteristics and quality of selected studies

Table 1 summarizes the characteristics of the included studies. Four different Gem-combination chemotherapy regimens were involved in the studies: Gem and cisplatin[10,11,18], Gem and S-1[12,13], Gem and oxaliplatin[17] and Gem and mitomycin C[14]. The effects of Gem-combination chemotherapy were compared with Gem monotherapy in three studies[10,12,18] and with other chemotherapy regimens in the remaining four studies[11,13,14,17]. The seven trials provided data from a total of 858 patients (mean: 123; range: 51 to 410). Males accounted for 17.9%-66% of all subjects, and the median patient age ranged from 47 to 75 years. All patients enrolled in the included studies had the following characteristics: histologically confirmed advanced local or metastatic biliary tract cancer not amenable to surgical resection; no previous chemotherapy; Eastern Cooperative Oncology Group Performance Status scores between 0 and 2; and adequate liver, renal and hematopoietic functions.

The details of grade 3-4 toxicity assessment are shown in Table 2 and include leukopenia, neutropenia, anemia, thrombocytopenia, increased alanine aminotransferase (ALT) level, nausea, vomiting, anorexia and diarrhea.

All seven eligible studies[10-14,17,18] were randomized, and two studies[13,14] described the method of randomization with definite descriptions. Allocation concealment was performed using a proprietary algorithm in one of the trials[13]. None of the trials reported double-blind procedures. Each trial included in the meta-analysis provided a detailed description of the number of and reasons for patient withdrawals and dropouts. Finally, two studies scored 4 points or above (Table 3).

DRR

The DRRs were reported in all studies and ranged from 9.4%-36.4% without significant inter-study heterogeneity (Q = 6.69, df = 6, I^2 = 10%). The pooled OR of the DRR estimated by the fixed effects model was 1.69

Table 1 Study characteristics

Ref.	Year	Treatment	*n*	Male (%)	Age mean (range), yr	DRR (%)	DCR (%)	PFS (mo)	OS (mo)
Valle *et al*[10]	2010	GEM + CIS	204	52.9	63.9 (32.8-81.9)	21.6	81.4	8.0	11.7
		GEM	206	52.4	63.2 (23.4-84.8)	15.5	71.8	5.0	8.0
Okusaka *et al*[18]	2010	GEM + CIS	41	43.9	65 (43-80)	19.5	68.3	5.8	11.2
		GEM	42	50.0	66.5 (49-78)	11.9	50.0	3.7	7.7
Sasaki *et al*[12]	2013	GEM + S-1	30	53.3	68 (47-83)	20.0	70.0	5.6	8.9
		GEM	32	66.7	75 (55-86)	9.4	62.5	4.3	9.2
Kornek *et al*[14]	2004	GEM + MMC	25	32.0	67 (44-75)	21.7	60.9	4.2	6.7
		MMC + CAPE	26	38.5	65 (45-75)	33.3	70.8	5.3	9.3
Sharma *et al*[17]	2010	GEM + OX	26	19.2	49	30.7	68.7	8.5	9.5
		FUFA	28	17.9	47	14.3	21.4	3.5	4.6
Kang *et al*[11]	2012	GEM + CIS	49	63.3	59 (32-77)	19.6	71.7	5.7	10.1
		S-1 + CIS	48	64.6	60 (36-77)	23.8	85.7	5.4	9.9
Morizane *et al*[13]	2013	GEM + S-1	50	54.0	66 (39-78)	36.4	59.1	7.1	12.5
		S-1	51	47.1	62.5 (49-79)	17.4	39.1	4.2	9.0

CAPE: Capecitabine; CIS: Cisplatin; DCR: Disease control rate; DRR: Disease response rate; FUFA: Fluorouracil-folinic acid; GEM: Gemcitabine; MMC: Mitomycin C; OS: Overall survival; OX: Oxaliplatin; PFS: Progression-free survival.

Table 2 Percentage of cases with grade 3 or 4 toxicity *n* (%)

Ref.	Treatment	Leukopenia	Neutropenia	Anemia	Thrombocytopenia	Increased ALT level	Nausea	Vomiting	Anorexia	Diarrhea
Valle *et al*[10]	GEM + CIS	15.7	25.3	7.6	8.6	9.6	4.0	5.1	3.0	NR
	GEM	9.5	16.6	3.0	6.5	17.1	3.5	5.5	2.5	NR
Okusaka *et al*[18]	GEM + CIS	29.3	56.1	36.6	39.0	24.4	0.0	0.0	0.0	2.4
	GEM	19.0	38.1	16.6	7.2	16.7	0.0	0.0	2.8	0.0
Sasaki *et al*[12]	GEM + S-1	33.0	33.0	10.0	7.0	3.0	3.0	0.0	3.0	0.0
	GEM	19.0	22.0	6.0	6.0	0.0	0.0	0.0	6.0	0.0
Kornek *et al*[14]	GEM + MMC	17.0	13.0	0.0	13.0	40.0	44.0	NR	NR	28.0
	MMC + CAPE	17.0	17.0	0.0	17.0	45.0	42.0	NR	NR	28.0
Sharma *et al*[17]	GEM + OX	38.5	38.5	38.5	10.0	15.4	NR	7.7	NR	NR
	FUFA	7.1	7.1	7.1	2.0	0.0	NR	7.1	NR	NR
Kang *et al*[11]	GEM + CIS	24.4	49.0	22.4	22.4	4.1	4.1	4.1	0.0	0.0
	S-1 + CIS	0.0	31.8	2.3	4.5	0.0	2.1	0.0	0.0	4.3
Morizane *et al*[13]	GEM + S-1	29.4	60.7	11.8	11.8	13.7	2.0	2.0	7.8	2.0
	S-1	2.0	4.0	4.0	4.0	12.0	4.0	0.0	6.0	6.0

ALT: Alanine aminotransferase; CAPE: Capecitabine; CIS: Cisplatin; FUFA: Fluorouracil-folinic acid; GEM: Gemcitabine; MMC: Mitomycin C; NR: No record; OX: Oxaliplatin.

Table 3 Jadad scores of the included studies

Study	Randomization	Concealed allocation	Double-blind	Complete description
Valle *et al*[10]	1	1	0	1
Okusaka *et al*[18]	1	1	0	1
Sasaki *et al*[12]	1	1	0	1
Kornek *et al*[14]	2	1	0	1
Sharm *et al*[17]	1	1	0	1
Kang *et al*[11]	1	1	0	1
Morizane *et al*[13]	2	2	0	1

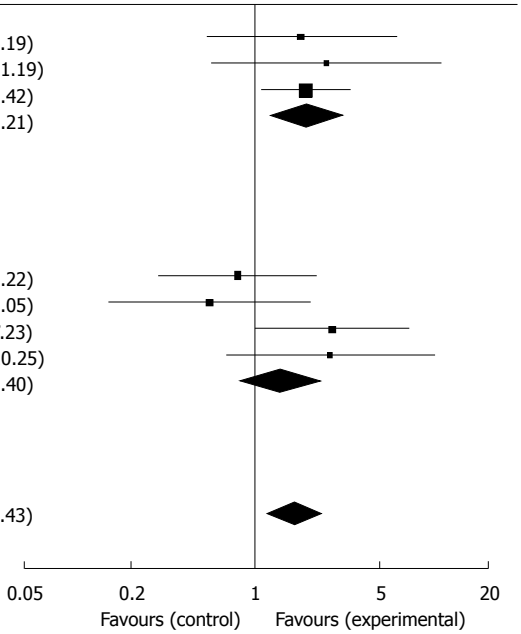
(95%CI: 1.17-2.43) (Figure 2A). The overall analysis revealed that the patients treated with Gem-based combinations achieved significantly higher DRR compared with the patients who had not received this combination chemotherapy (P = 0.01). A subgroup analysis indicated that the DRR was significantly higher for the patients treated with Gem-based combination chemotherapy compared with the patients treated with Gem alone (OR = 1.97, 95%CI: 1.20-3.21; P = 0.01). The OR for the non-Gem-based chemotherapy subgroup was 1.39 (95%CI: 0.82-2.40), which was not statistically significant.

DCR

The DCR in the studies ranged from 21.4%-86.0%. Significant heterogeneity was detected between the studies (Q = 16.57, df = 6, I^2 = 64%; P = 0.01), therefore, a random effects model was used for the meta-analysis of the DCR. The total OR for the DCR was 1.65 (95%CI: 0.91-3.00; P = 0.10) (Figure 2B). The results of the subgroup analyses indicated that the patients treated with Gem-based combinations had significantly higher DCRs compared with the patients treated with Gem alone (OR = 1.82, 95%CI: 1.18-2.81; P = 0.01). The DCR of the non-Gem-based chemotherapy subgroup was lower compared with the Gem-based combination chemotherapy group (OR = 1.48, 95%CI: 0.43-5.07), but the difference was not sig-

A

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, fixed, 95%CI
1.1.1 Gem-based *vs* Gem						
Okusaka *et al*[18]	8	37	5	38	8.5%	1.82 (0.54, 6.19)
Sasaki *et al*[12]	6	29	3	32	5.0%	2.52 (0.57, 11.19)
Valle *et al*[10]	42	161	22	142	38.0%	1.93 (1.08, 3.42)
Subtotal (95%CI)		227		212	51.5%	1.97 (1.20, 3.21)
Total events	56		30			
Heterogeneity: $\chi^2 = 0.13$, $df = 2$ ($P = 0.94$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.70$ ($P = 0.007$)						
1.1.2 Gem-based *vs* non-Gem-based						
Kang *et al*[11]	9	46	10	43	18.3%	0.80 (0.29, 2.22)
Kornek *et al*[14]	5	23	8	24	13.5%	0.56 (0.15, 2.05)
Morizane *et al*[13]	16	44	8	46	10.9%	2.71 (1.02, 7.23)
Sharma *et al*[17]	8	26	4	28	5.9%	2.67 (0.69, 10.25)
Subtotal (95%CI)		139		141	48.5%	1.39 (0.81, 2.40)
Total events	38		30			
Heterogeneity: $\chi^2 = 5.72$, $df = 3$ ($P = 0.13$); $I^2 = 48\%$						
Test for overall effect: $Z = 1.19$ ($P = 0.24$)						
Total (95%CI)		366		353	100.0%	1.69 (1.17, 2.43)
Total events	94		60			
Heterogeneity: $\chi^2 = 6.69$, $df = 6$ ($P = 0.35$); $I^2 = 10\%$						
Test for overall effect: $Z = 2.82$ ($P = 0.005$)						
Test for subgroup differences: $\chi^2 = 0.86$, $df = 1$ ($P = 0.35$); $I^2 = 0\%$						



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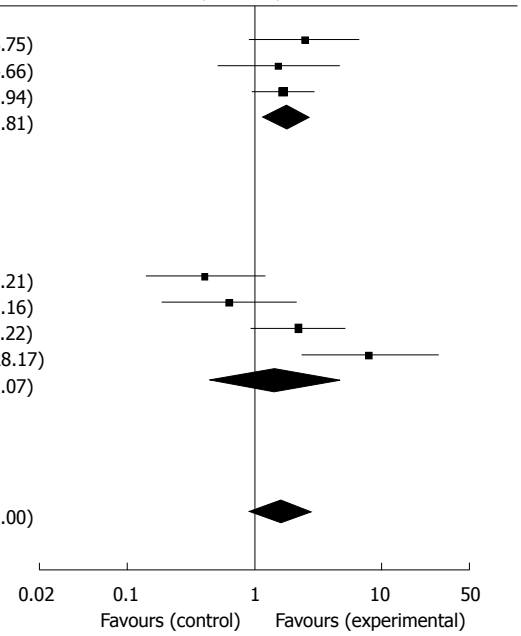
Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95%CI
1.2.1 Gem-based *vs* Gem						
Okusaka *et al*[18]	28	37	21	38	14.3%	2.52 (0.94, 6.75)
Sasaki *et al*[12]	21	29	20	32	13.2%	1.57 (0.53, 4.66)
Valle *et al*[10]	131	161	102	142	19.7%	1.71 (1.00, 2.94)
Subtotal (95%CI)		227		212	47.1%	1.82 (1.18, 2.81)
Total events	180		143			
Heterogeneity: $\text{Tau}^2 = 0.00$, $\chi^2 = 0.53$, $df = 2$ ($P = 0.77$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.71$ ($P = 0.007$)						
1.2.2 Gem-based *vs* non-Gem-based						
Kang *et al*[11]	33	46	37	43	13.3%	0.41 (0.14, 1.21)
Kornek *et al*[14]	14	23	17	24	11.9%	0.64 (0.19, 2.16)
Morizane *et al*[13]	26	44	18	46	16.0%	2.25 (0.97, 5.22)
Sharma *et al*[17]	18	26	6	28	11.7%	8.25 (2.42, 28.17)
Subtotal (95%CI)		139		141	52.9%	1.48 (0.43, 5.07)
Total events	91		78			
Heterogeneity: $\text{Tau}^2 = 1.27$, $\chi^2 = 15.72$, $df = 3$ ($P = 0.001$); $I^2 = 81\%$						
Test for overall effect: $Z = 0.62$ ($P = 0.53$)						
Total (95%CI)		366		353	100.0%	1.65 (0.91, 3.00)
Total events	271		221			
Heterogeneity: $\text{Tau}^2 = 0.39$, $\chi^2 = 16.57$, $df = 6$ ($P = 0.01$); $I^2 = 64\%$						
Test for overall effect: $Z = 1.66$ ($P = 0.10$)						
Test for subgroup differences: $\chi^2 = 0.10$, $df = 1$ ($P = 0.76$); $I^2 = 0\%$						



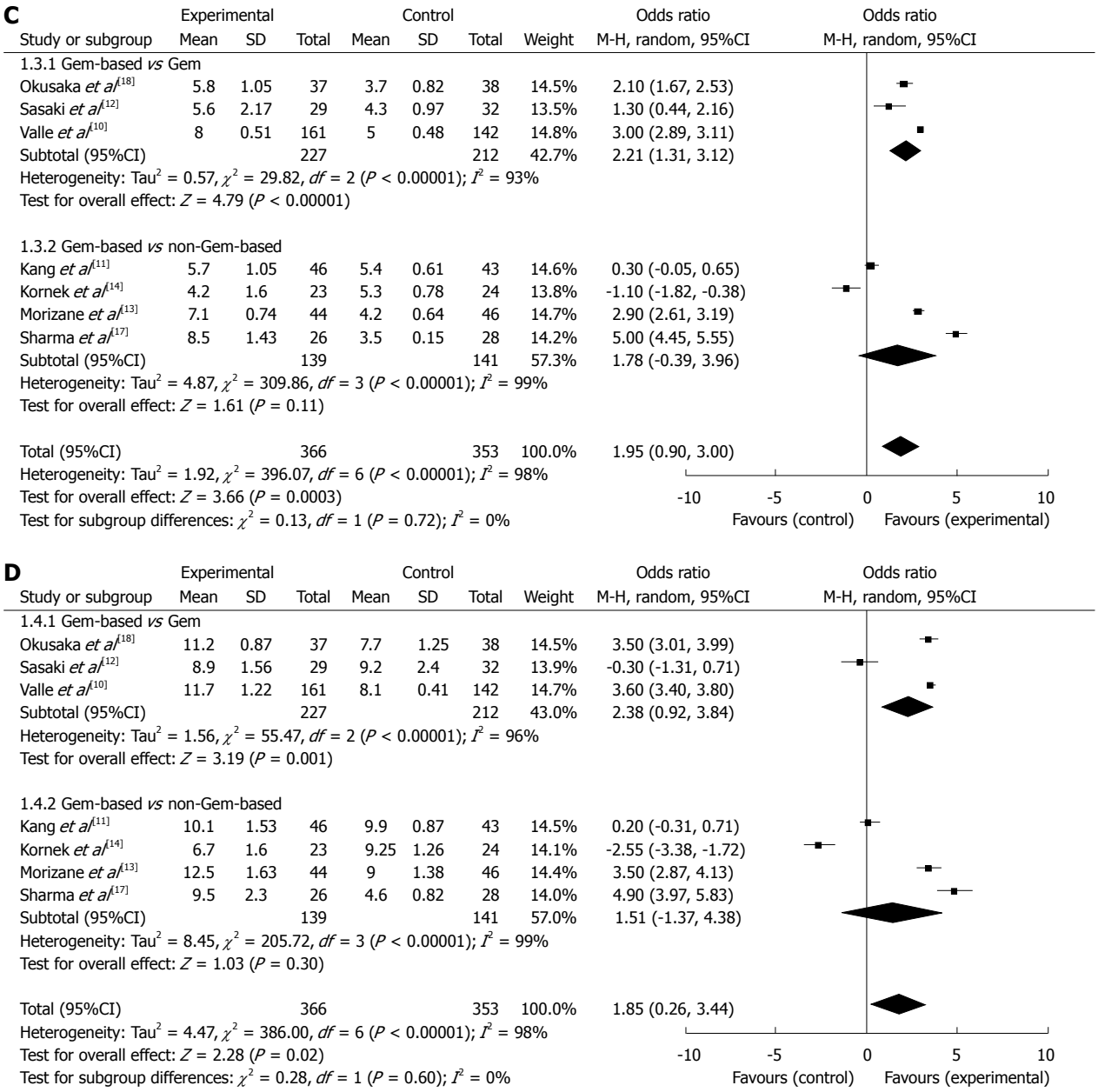


Figure 2 Forest plots of the effects of gemcitabine-based combination chemotherapy in patients with biliary tract cancer. A: Disease response rate; B: Disease control rate; C: Progression-free survival; D: Overall survival. Gem: Gemcitabine monotherapy; Gem-based: Gem-based combination chemotherapy; non-Gem-based: non-Gemcitabine-based chemotherapy.

nificant.

PFS

The median PFS of the included studies ranged from 3.5-8.5 mo. After data pooling, significant heterogeneity was observed among the studies (Q = 396.07, df = 6, I^2 = 98%; P = 0.00), therefore, a random effects model was used for the meta-analysis of the median PFS. The overall MD for the PFS was 1.95 (95%CI: 0.90-3.00; P = 0.00) (Figure 2C), which suggests that Gem-based combination chemotherapy significantly improved patient PFS. A subgroup analysis also revealed that the PFS was significantly longer for the patients treated with Gem-based combination chemotherapy compared with the patients treated with Gem alone (MD = 2.21, 95%CI: 1.31-3.12; P = 0.00). The MD for Gem-based *vs* non-Gem-based chemotherapy was 1.78 (95%CI: -0.39-3.96), but was not significantly different.

OS

The median OS ranged from 4.6-12.5 mo. Significant heterogeneity was detected between the studies (Q = 386.00, df = 6, I^2 = 98%; P = 0.00), therefore, a random effects model was used for the meta-analysis of OS. The overall MD for the OS was 1.85 (95%CI: 0.26-3.44; P = 0.02) (Figure 2D), which indicated that Gem-based combination chemotherapy significantly prolonged the overall survival time. A subgroup analysis revealed that the OS

was significantly longer for the patients treated with Gem-based combination therapy compared with the patients treated with Gem alone (MD = 2.38, 95%CI: 0.92-3.84; $P = 0.00$). The OS of the Gem-based combination chemotherapy group was longer compared with the non-Gem-based chemotherapy group (MD = 1.51, 95%CI: -1.37-4.38), but the difference was not significant.

Toxicities

The results of the meta-analysis of the main toxicities are presented in Figure 3. The ORs for grade 3-4 hematological toxicities analyzed in this study were higher in the Gem-based combination chemotherapy group compared with the Gem monotherapy and non-Gem-based chemotherapy groups. The incidence of leukopenia (OR = 2.98, 95%CI: 1.44-6.20; $P = 0.00$), anemia (OR = 2.96, 95%CI: 1.79-4.92; $P = 0.00$) and neutropenia (OR = 2.80, 95%CI: 1.39-5.64; $P = 0.00$) were all significantly different between the treatment groups, whereas no significant difference was noted for thrombocytopenia (OR = 1.71; 95%CI: 0.75-3.89). No significant difference in the increased ALT level (OR = 0.87; 95%CI: 0.58-1.30) was found between the treatment groups.

In the subgroup analysis, the ORs were 1.82-7.01 for leukopenia, 1.96-7.04 for anemia, 1.78-4.63 for neutropenia, 1.13-2.79 for thrombocytopenia, and 0.76-1.11 for the increased ALT level. There were significant differences between the Gem-based combination chemotherapy group and the Gem monotherapy group in leukopenia ($P = 0.01$), anemia ($P = 0.03$) and neutropenia ($P = 0.01$), but not thrombocytopenia or the increased ALT level. The ORs of leukopenia (OR = 7.17; $P = 0.02$) and anemia (OR = 7.04; $P = 0.00$) in the Gem-based combination chemotherapy group were over seven times greater than those in the non-Gem-based chemotherapy subgroup; no significant differences were observed for the other toxicities.

Sources of heterogeneity and sensitivity analysis

Because significant heterogeneity was detected among the studies for the DCR, PFS and OS, we performed a sensitivity analysis to explore the heterogeneity by omitting one study at a time and calculating pooled ORs for the remainder of the studies. The study by Kang *et al*[11] may have been the key contributor to the inter-study heterogeneity in the DCR meta-analysis. No heterogeneity was observed after excluding this study ($Q = 9.26$, $df = 5$, $I^2 = 46\%$; $P = 0.10$); the pooled OR for the DCR was 2.03 (95%CI: 1.21-3.40). The direction and magnitude of the pooled OR for the PFS and the pooled MD for the OS did not vary markedly with the removal of any study, which indicated good reliability (data not shown).

Publication bias

Egger's test was used to investigate potential publication bias; there was no evidence of bias for the DRR ($P = 1.00$), DCR ($P = 0.23$), PFS ($P = 0.55$), or OS ($P = 1.00$). Additionally, publication bias was not indicated by a Begg's funnel plot (Figure 4).

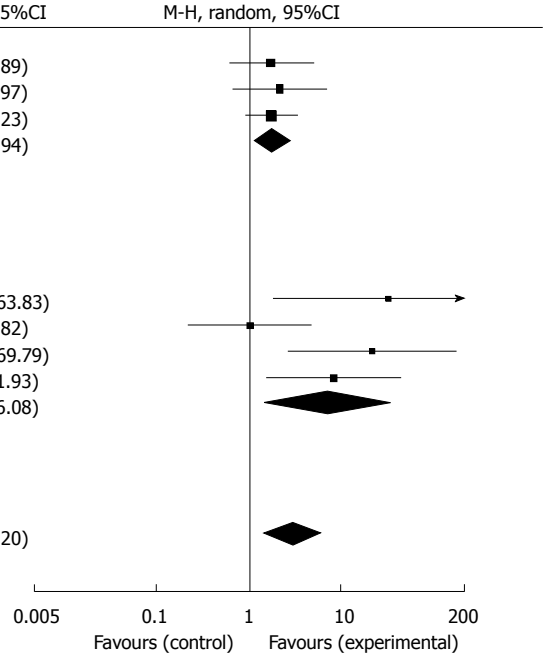
DISCUSSION

BTC is a heterogeneous group of relatively rare tumors, which often have extremely poor prognoses. Most patients present with locally advanced or metastatic disease and are candidates for surgical resection; as a result, many patients must rely on palliative chemotherapy as the only treatment option. During the last decade, several randomized controlled clinical trials have evaluated gemcitabine in combination with various agents in an attempt to improve the prognosis of advanced BTC. In this meta-analysis, we systematically evaluated the efficacy and safety of Gem-based combination chemotherapy in the treatment of advanced BTC. Our findings suggest that patients treated with Gem-based combination chemotherapy may experience better survival outcomes compared with patients not treated with this combination. However, Gem-combination chemotherapy regimens were not identical in all included studies; thus, our findings must be considered in light of this limitation.

Our overall analysis revealed that the patients treated with Gem-based combination chemotherapy had a significantly greater DRR as well as a longer PFS and OS compared with the patients not treated with this combination. Heterogeneity among the studies may be a reason for the lack of statistically significant data related to the DCR. Furthermore, the subgroup analysis revealed that the treatment with Gem-based combination chemotherapy was associated with significantly better DRR, DCR, PFS and OS outcomes compared with treatment with Gem alone. Our findings are consistent with those of Eckel *et al*[22], who conducted a meta-analysis of chemotherapy trials for advanced BTC treatment and reported that Gem-based combination chemotherapy (Gem-cisplatin or Gem-oxaliplatin) was associated with the highest DRRs and tumor control rates. However, their meta-analysis was not restricted to randomized trials. Another recent meta-analysis by Yang *et al*[23] including three randomized trials indicated that the patients with advanced BTC who were treated with Gem-based combination chemotherapy (Gem plus platinum agents) experienced better survival outcomes compared with the patients not treated with this chemotherapy combination. However, the analysis involved studies that evaluated Gem plus platinum chemotherapy; thus, new treatments, such as Gem plus S-1, were not included. A review published by Serrano *et al*[24] also suggested that Gem alone or in combination with other agents showed a better response rate that correlated with the time to progression. Additionally, regimens that contained two drugs induced higher response rates compared with single agent treatments. In our study, the subgroup analysis also indicated that Gem-based combination chemotherapy provides some benefit over non-Gem-based chemotherapy, but the result was not significant. The consistency between our findings and previous analyses further supports the use of Gem-based combination chemotherapy as a

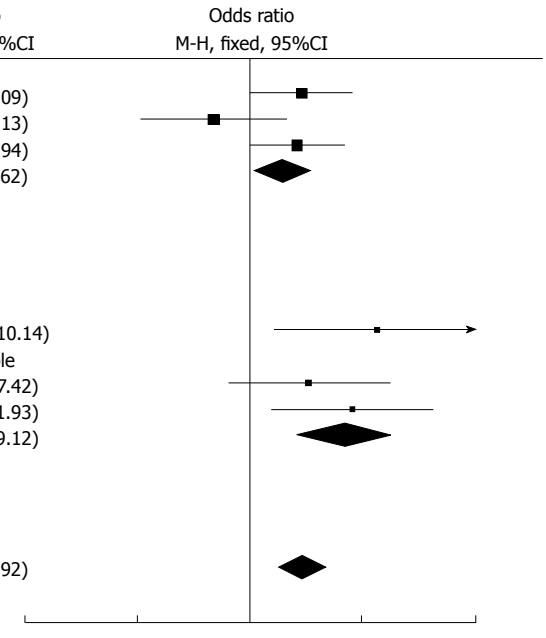
A

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95%CI
2.1.1 Gem-based *vs* Gem						
Okusaka *et al*[18]	12	41	8	42	18.9%	1.76 (0.63, 4.89)
Sasaki *et al*[12]	10	30	6	32	17.0%	2.17 (0.67, 6.97)
Valle *et al*[10]	31	198	19	199	24.9%	1.76 (1.96, 3.23)
Subtotal (95%CI)		269		273	60.8%	1.82 (1.13, 2.94)
Total events	53		33			
Heterogeneity: Tau^2 = 0.00, χ^2 = 0.10, *df* = 2 (*P* = 0.95); I^2 = 0%						
Test for overall effect: *Z* = 2.46 (*P* = 0.01)						
2.1.2 Gem-based *vs* non-Gem-based						
Kang *et al*[11]	12	49	0	48	5.4%	32.33 (1.85, 563.83)
Kornek *et al*[14]	4	23	4	24	13.1%	1.05 (0.23, 4.82)
Morizane *et al*[13]	15	50	1	51	8.8%	21.43 (2.70, 169.79)
Sharma *et al*[17]	10	26	2	28	12.0%	8.13 (1.57, 41.93)
Subtotal (95%CI)		148		151	39.2%	7.17 (1.43, 36.08)
Total events	41		7			
Heterogeneity: Tau^2 = 1.69, χ^2 = 8.32, *df* = 3 (*P* = 0.04); I^2 = 64%						
Test for overall effect: *Z* = 2.39 (*P* = 0.02)						
Total (95%CI)		417		424	100.0%	2.98 (1.44, 6.20)
Total events	94		40			
Heterogeneity: Tau^2 = 0.46, χ^2 = 12.94, *df* = 6 (*P* = 0.04); I^2 = 54%						
Test for overall effect: *Z* = 2.93 (*P* = 0.003)						
Test for subgroup differences: χ^2 = 2.54, *df* = 1 (*P* = 0.11); I^2 = 60.7%						



B

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, fixed, 95%CI
2.2.1 Gem-based *vs* Gem						
Okusaka *et al*[18]	15	41	7	42	23.3%	2.88 (1.03, 8.09)
Sasaki *et al*[12]	3	30	6	32	27.7%	0.48 (0.11, 2.13)
Valle *et al*[10]	15	198	6	199	29.3%	2.64 (1.00, 6.94)
Subtotal (95%CI)		269		273	80.3%	1.96 (1.07, 3.62)
Total events	33		19			
Heterogeneity: χ^2 = 4.32, *df* = 2 (*P* = 0.12); I^2 = 54%						
Test for overall effect: *Z* = 2.17 (*P* = 0.03)						
2.2.2 Gem-based *vs* non-Gem-based						
Kang *et al*[11]	11	49	1	48	4.2%	13.61 (1.68, 110.14)
Kornek *et al*[14]	0	23	0	24		Not estimable
Morizane *et al*[13]	6	50	2	51	9.2%	3.34 (0.64, 17.42)
Sharma *et al*[17]	10	26	2	28	6.3%	8.13 (1.57, 41.93)
Subtotal (95%CI)		148		151	19.7%	7.04 (2.59, 19.12)
Total events	27		5			
Heterogeneity: χ^2 = 1.19, *df* = 2 (*P* = 0.55); I^2 = 0%						
Test for overall effect: *Z* = 3.83 (*P* = 0.00001)						
Total (95%CI)		417		424	100.0%	2.96 (1.79, 4.92)
Total events	60		24			
Heterogeneity: χ^2 = 9.31, *df* = 5 (*P* = 0.10); I^2 = 46%						
Test for overall effect: *Z* = 4.21 (*P* < 0.0001)						
Test for subgroup differences: χ^2 = 4.56, *df* = 1 (*P* = 0.03); I^2 = 78.1%						



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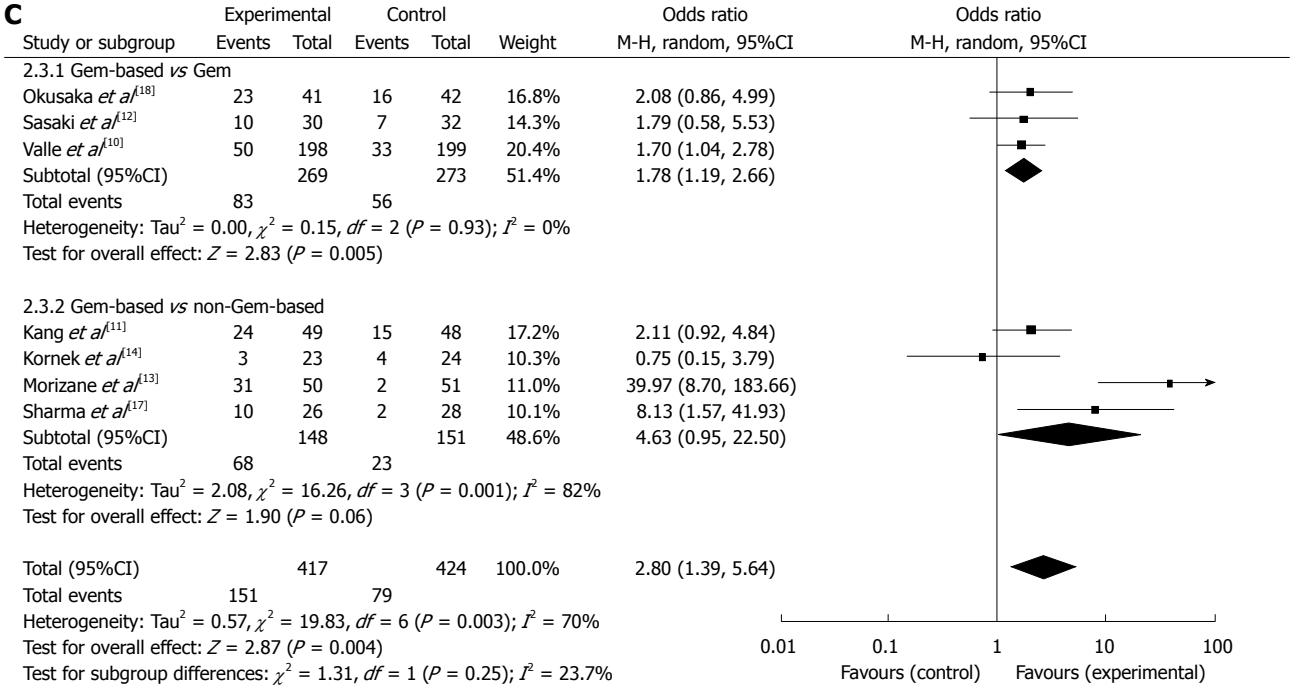
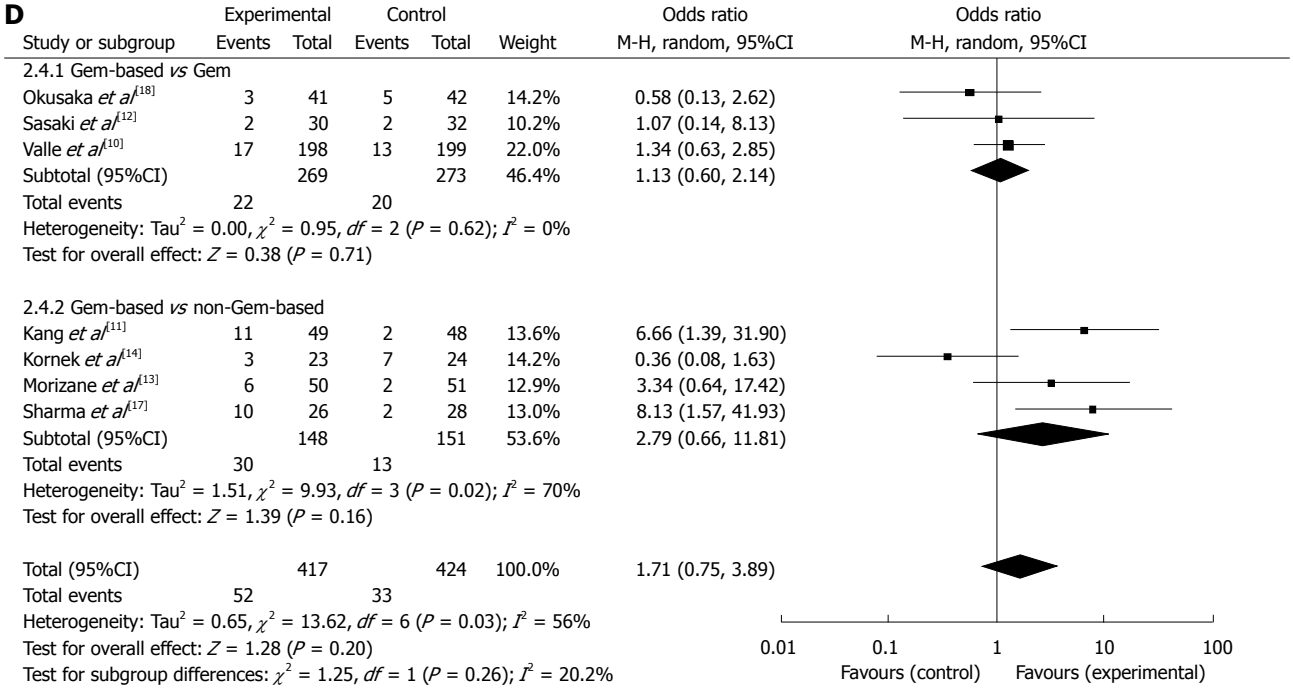

Experimental
Control
Odds ratio
Odds ratio
Study or subgroup Events Total Events Total Weight M-H, random, 95%CI
M-H, random, 95%CI
2.3.1 Gem-based vs Gem
Okusaka et al[18] 23 41 16 42 16.8% 2.08 (0.86, 4.99)
Sasaki et al[12] 10 30 7 32 14.3% 1.79 (0.58, 5.53)
Valle et al[10] 50 198 33 199 20.4% 1.70 (1.04, 2.78)
Subtotal (95%CI) 269 273 51.4% 1.78 (1.19, 2.66)
Total events 83 56
Heterogeneity: Tau² = 0.00, χ² = 0.15, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.83 (P = 0.005)
2.3.2 Gem-based vs non-Gem-based
Kang et al[11] 24 49 15 48 17.2% 2.11 (0.92, 4.84)
Kornek et al[14] 3 23 4 24 10.3% 0.75 (0.15, 3.79)
Morizane et al[13] 31 50 2 51 11.0% 39.97 (8.70, 183.66)
Sharma et al[17] 10 26 2 28 10.1% 8.13 (1.57, 41.93)
Subtotal (95%CI) 148 151 48.6% 4.63 (0.95, 22.50)
Total events 68 23
Heterogeneity: Tau² = 2.08, χ² = 16.26, df = 3 (P = 0.001); I² = 82%
Test for overall effect: Z = 1.90 (P = 0.06)
Total (95%CI) 417 424 100.0% 2.80 (1.39, 5.64)
Total events 151 79
Heterogeneity: Tau² = 0.57, χ² = 19.83, df = 6 (P = 0.003); I² = 70%
Test for overall effect: Z = 2.87 (P = 0.004)
Test for subgroup differences: χ² = 1.31, df = 1 (P = 0.25); I² = 23.7%
0.01 0.1 1 10 100
Favours (control) Favours (experimental)

D


Experimental
Control
Odds ratio
Odds ratio
Study or subgroup Events Total Events Total Weight M-H, random, 95%CI
M-H, random, 95%CI
2.4.1 Gem-based vs Gem
Okusaka et al[18] 3 41 5 42 14.2% 0.58 (0.13, 2.62)
Sasaki et al[12] 2 30 2 32 10.2% 1.07 (0.14, 8.13)
Valle et al[10] 17 198 13 199 22.0% 1.34 (0.63, 2.85)
Subtotal (95%CI) 269 273 46.4% 1.13 (0.60, 2.14)
Total events 22 20
Heterogeneity: Tau² = 0.00, χ² = 0.95, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.71)
2.4.2 Gem-based vs non-Gem-based
Kang et al[11] 11 49 2 48 13.6% 6.66 (1.39, 31.90)
Kornek et al[14] 3 23 7 24 14.2% 0.36 (0.08, 1.63)
Morizane et al[13] 6 50 2 51 12.9% 3.34 (0.64, 17.42)
Sharma et al[17] 10 26 2 28 13.0% 8.13 (1.57, 41.93)
Subtotal (95%CI) 148 151 53.6% 2.79 (0.66, 11.81)
Total events 30 13
Heterogeneity: Tau² = 1.51, χ² = 9.93, df = 3 (P = 0.02); I² = 70%
Test for overall effect: Z = 1.39 (P = 0.16)
Total (95%CI) 417 424 100.0% 1.71 (0.75, 3.89)
Total events 52 33
Heterogeneity: Tau² = 0.65, χ² = 13.62, df = 6 (P = 0.03); I² = 56%
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: χ² = 1.25, df = 1 (P = 0.26); I² = 20.2%
0.01 0.1 1 10 100
Favours (control) Favours (experimental)

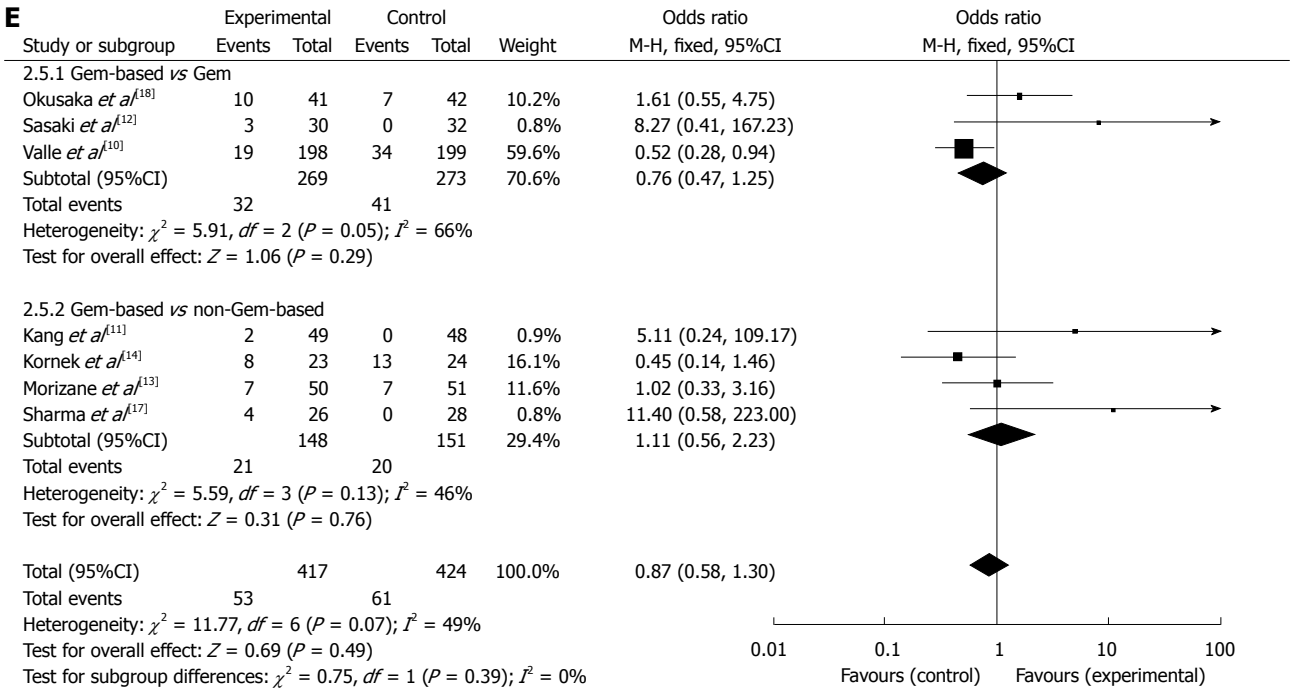


Figure 3 Forest plots of the main toxicities of gemcitabine-based combination chemotherapy in patients with biliary tract cancer. A: Leukopenia; B: Anemia; C: Neutropenia; D: Thrombocytopenia; E: Increased alanine aminotransferase level. Gem: gemcitabine monotherapy; Gem-based: Gem-based combination chemotherapy; non-Gem-based: non-Gem-based chemotherapy.

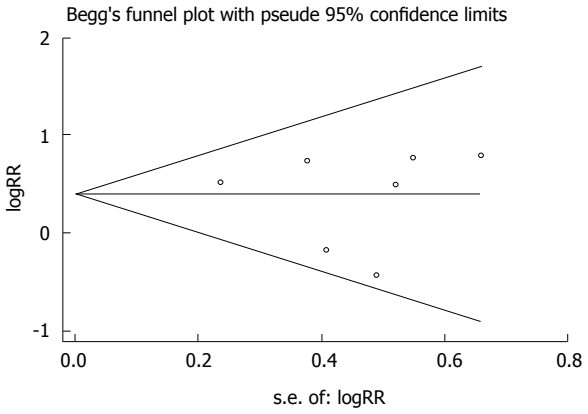


Figure 4 Begg's funnel plot for the assessment of publication bias.

first-line treatment for advanced BTC.

We also assessed the five most common toxicities related to the chemotherapeutic treatment of advanced BTC, which are leukopenia, neutropenia, anemia, thrombocytopenia and an increased ALT level. The analysis indicated that the incidence of grade 3-4 hematological toxicities, including leukopenia, neutropenia and anemia, were significantly higher following Gem-based combination chemotherapy than following Gem monotherapy or non-Gem-based chemotherapy. There was no significant difference in the rates of thrombocytopenia or the increased ALT level. Furthermore, a subgroup analysis showed that the ORs of leukopenia, neutropenia and anemia after treatment with Gem-based combination chemotherapy were almost twice those of Gem monotherapy. Additionally, the ORs of leukopenia and neutropenia in the Gem-based combination chemotherapy were more than seven times those of the non-Gem-based chemotherapy. The results presented here suggest that Gem-based combination chemotherapy induced more toxicity compared with Gem alone or non-Gem-based chemotherapy. However, all severe hematological toxicities (grade 3 or 4) are infrequent and reversible, and these results are consistent with a previous study[24].

Several limitations of our meta-analysis should be mentioned. First, only randomized trials were selected; thus, the total included sample size was small (seven studies). Additionally, our selections may have been subjected to some bias, although we observed none. Second, our data are based on the published data for which the patient outcomes according to the type of BTC were not available. This may limit our capacity to fully explore the effects of Gem-based combination chemotherapy in different types of BTC. Another limitation was that the included studies did not have homogenous characteristics with respect to the regimens used for Gem-based combination chemotherapy or the competing regimen. Furthermore, the patient demographics between the included studies were different. Due to the limitations mentioned above, the results of this meta-analysis should be interpreted with care.

In conclusion, the results of our meta-analysis of randomized trials suggest that the treatment of advanced BTC with Gem-based combination chemotherapy is associated with significantly better survival outcomes compared with treatment with Gem alone or non-Gem-based chemotherapy. Major hematological toxicities associated with Gem-based combination chemotherapy were

generally manageable and acceptable. Therefore, Gem-based combination chemotherapy should be considered as a standard first-line treatment for advanced BTC. In the future, larger multicenter randomized controlled trials should be designed to examine the efficacy and safety of Gem-based combination chemotherapy.

COMMENTS

Background

Biliary tract cancer (BTC) is a heterogeneous group of relatively rare tumors that often have extremely poor prognoses. Gemcitabine (Gem) is the treatment of choice for patients with advanced BTC. The results from several phase Ⅱ studies suggest that Gem, alone or in combination with other agents, has been relatively effective for treating BTC. However, most of these studies were small, single-arm and nonrandomized trials.

Research frontiers

The data from the largest randomized trial to date indicated that the overall survival of BTC patients was significantly higher in the Gem and cisplatin arm *vs* the Gem single-agent arm. Since that time, several randomized trials comparing Gem-based combination chemotherapy with other regimens have been published. However, the results of these trials were conflicting, which has made the role of Gem-based combination chemotherapy controversial.

Innovations and breakthroughs

Based on this meta-analysis, Gem-based combination chemotherapy was superior in disease response rate, progression-free survival and overall survival to the radiation therapy group or chemotherapy group alone. Similar results were indicated in the subgroup analyses. The Gem-based combination chemotherapy group had significantly more grade 3-4 treatment-related hematologic and non-hematologic toxicities than Gem alone or non-Gem-based chemotherapy groups. These findings were not presented clearly in previous systematic reviews.

Applications

The results of this meta-analysis of randomized trials suggest that Gem-based combination chemotherapy can improve the prognosis of patients with advanced BTC, though it may also increase the treatment-related toxicity.

Peer review

This is a well-written manuscript analyzing therapeutic management of advanced biliary tract cancer. In this manuscript, the authors compared the efficacy and safety of Gem-based combination chemotherapy with Gem alone or non-Gem-based chemotherapy. The data were collected and analyzed effectively.

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