RESEARCH ARTICLE

Gemcitabine Alone or in Combination with Cisplatin for Advanced Biliary Tract Carcinomas: an Overview of Clinical Evidence

Tian-Tian Sun, Ji-Lin Wang, Jing-Yuan Fang*

Abstract

Background and Objective: There has been no universally agreed standard chemotherapy regimen for patients with advanced biliary tract carcinomas (BTC). We aimed to fully display and evaluate the clinical evidence for gemcitabine or gemcitabine-cisplatin combination for advanced BTC. Methods: Systematic searches were performed to identify relevant randomized controlled trials (RCTs) and uncontrolled trials. Overall survival (OS), progression-free survival (PFS), overall response rates (ORR), tumor control rates (TCR), and toxicity were evaluated. Evidence levels of the results were evaluated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Results: Results of the eleven gemcitabine-cisplatin trials and ten gemcitabine trials showed both chemotherapy regimens had benefits with reference to mean OS (8.63 vs. 8.79 months), mean PFS (4.86 vs. 4.72 months), pooled ORR (25.3% vs. 19.6%) and TCR (55.2% vs. 53.1%). Two RCTs showed the gemcitabine-cisplatin combination to prolong the mean PFS (mean difference [MD] 2.57, 95%CI 1.69 3.45), substantially increasing the mean OS (MD 3.59, 95% CI 3.48 3.71), and producing a similar effect in ORR (risk ratio [RR] 1.59, 95%CI 1.04 2.43), increasing TCR (RR 1.15, 95%CI 1.02 1.31) compared with gemcitabine alone, with generally manageable grade 3 or 4 adverse events. The evidence level of OS was moderate, and other outcomes (ORR, PFS, TCR, anaemia, neutropenia) were at low evidence levels. Conclusion: Available evidence was limited with low quality, which showed that both gemcitabine-cisplatin and gemcitabine alone had clinical activity with acceptable safety profiles, and gemcitabine-cisplatin appeared to be more useful for advanced BTC patients than gemcitabine alone.

Keywords: Biliary tract neoplasms - gemcitabine - cisplatin - combination therapy

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Introduction

Biliary tract carcinomas (BTC), comprising gallbladder carcinoma (GBC) and cholangiocarcinoma (CC), are rare tumors, accounting for less than 5% of cancers, and have poor prognosis and high mortality (Delbaldo et al., 2009). Over the past several decades, the rates of BTC have been rising worldwide (Patel, 2002). Surgical resection is considered as the only potentially curative choice for treatment. Unfortunately, most BTC are diagnosed at advanced stages and unresectable. Even if the tumors are detected earlier, some are inoperable because the tumor sites are often contiguous with important organs and infiltrate into these tissues (Levy et al., 2001). In patients undergoing aggressive surgery, 5-year survival rates are only 5%-10% for GBC and 10%-40% for CC. The condition was much worse for patients unsuitable for surgery, whose survival expectation is limited to 6 months (Groen et al., 1999).

Palliative chemotherapy is an option for patients with advanced (inoperable, recurrent or metastatic) BTC. In the past years, 5-FU alone or in combination with mitomycin C, cisplatin, hydroxyurea, or methotrexate were used for the majority of BTC patients, but the response rates were disappointing (Smith et al., 1984; Gebbia et al., 1996; Ducreu et al., 1998; Patt et al., 2001). Researchers had to find new drugs for this carcinoma. Gemcitabine, a deoxycytidine derivative, which inhibits DNA elongation through intracellular phosphorylation of ribonucleotide reductase, has been proved active in the treatment of pancreatic cancer (Bergman et al., 1996; Levy et al., 2001; Comella et al..2001). Considering the histological common origin of the pancreas and biliary tract (Gallardo et al., 1998), gemcitabine is supposed to be one of the most promising drugs for BTC. Studies showed that gemcitabine in combination with cisplatin, a stable platinum complex, were more effective than gemcitabine alone for a number of different tumors, such as lung cancer, bladder cancer, pancreatic cancer, and head and neck cancer (Crino et al., 1995; Hitt et al., 1998; Von et al., 2005; Heinrich et al., 2008). Some trials were conducted to evaluate the roles of gemcitabine or gemcitabine-cisplatin combination for advanced BTC. However, most studies were phase II trials and only few RCTs were conducted

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because of the low incidence rate and the high mortality. Those trials usually recruited small number of participants and their conclusions were conflicting. So we conducted this overview, with the purpose of fully displaying the clinical evidence of gemcitabine or gemcitabine-cisplatin combination for advanced BTC, and comparing gemcitabine-cisplatin combination with gemcitabine alone for advanced BTC in order to provide advice for clinical therapy of this disease.

Materials and Methods

Search strategy

Systematic literature searches were performed in PubMed, the Cochrane Library, Embase, and ISI Web of Knowledge using gemcitabine, cisplatin, biliary tract cancer (carcinoma, tumor), bile duct cancer (carcinoma, tumor), gallbladder carcinoma, and cholangiocarcinoma. Additionally, we performed manual search using reference lists of original articles and previous reviews. Online clinical trial registers, such as ClinicalTrials.gov, and international oncological conferences were also searched. All searches were conducted in August 2012 and updated in November 2012 without language restrictions.

Inclusion and exclusion criteria

RCTs comparing gemcitabine-cisplatin with gemcitabine in the treatment of advanced BTC patients were included. At the same time, we also included clinical trials reporting the efficacy of gemcitabine alone or in combination with cisplatin for advanced BTC patients. But letters, comments, editorials, and practice guidelines were excluded.

Study selection and data collection

Two authors (TT Sun, JL Wang) independently screened all titles and abstracts, and selected studies according to the predetermined eligibility criteria after retrieving all potential full texts. Basic information and key characteristics of the trials, including study design, countries, participants, interventions, and outcomes were extracted. Disagreements were resolved by consulting with a third reviewer (JY Fang).

Data analysis

Overall survival (OS), progression-free survival (PFS), overall response rates (ORR=complete response (CR) +partial response (PR)), tumor control rates (TCR=stable disease (SD) + CR + PR), and toxicity (according to the National Cancer Institute common toxicity criteria) were assessed.

For the data from uncontrolled studies, statistical analyses were conducted using SPSS version 15.0 for Windows. For dichotomous outcomes, data were pooled by summarizing the number of events and patients of the trials, and computed as the sum of the responders divided by the sum of the patients, such as pooled ORR and TCR. 95% confidence intervals (CI) were calculated using the method of Clopper and Pearson. For continuous outcomes, mean values were calculated, such as mean PFS and mean OS.

Methodological qualities of the included RCTs were evaluated by two independent reviewers (TT Sun & JL Wang) using Handbook 5.0 recommended standards (Higgins et al., 2008) based on the following items: randomization, concealed allocation, selective reporting, incomplete outcome data, intention to treatment analysis, and other biases. RevMan software 5.0 was used for statistical analysis based an intention-to-treat method. For dichotomous outcomes, the results were expressed as risk ratio (RR) with 95%CI. If there were continuous scales of measurement, the mean difference (MD) was used to assess the effects of treatment. Heterogeneity was analyzed using an I^2 test with n-1 degrees of freedom, and with an α-value of 0.05 used for statistical significance. An I^2 estimate greater than 50% ($P < 0.05$) was regarded as indicating a high level of heterogeneity and the causes were investigated. According to the level of heterogeneity between trials, either fixed or random effects models were used.

For assessing the level of the evidence concluded from the RCTs, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Schunemann et al., 2006; Akl et al., 2008). The GRADE approach specifies four levels of quality: high, moderate, low, and very low quality evidence, which indicate different quality of the results. We produced Summary of Findings (SoF) tables, which would present the main findings of SR and provide key information concerning available data on all outcomes, the effect of the intervention, and the quality of evidence.

Results

Search results

After systematic searches, we identified 203 potentially relevant papers. After screening abstracts and titles, we excluded 164 citations. At the same time, 4 citations were found by reference tracking. After screening full texts of the 43 papers, we excluded traditional reviews (n=5), non-clinical trials (n=5) and studies on other drugs (n=9). As for the different articles published on the results of the same trial, we only included the recently published one (excluding 1). Finally, 23 trials (Metzger et al., 1998; Valencak et al., 2000; Gallardo et al., 2001; Penz et al., 2001; Lin et al., 2003; Eng et al., 2004; Doval et al., 2004;

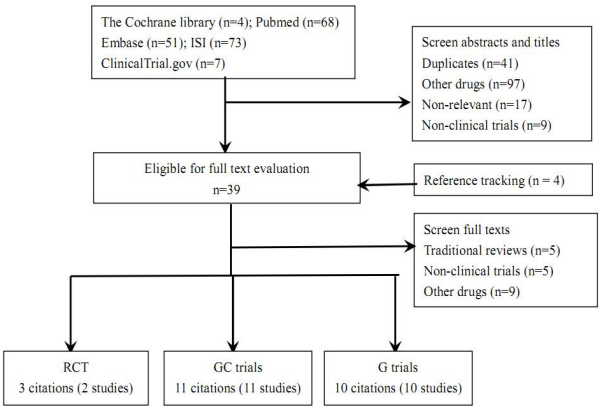

Figure 1. Flow Diagram of Search Strategy and Review Process

Table 1. Characteristics of Included Studies

Study	Country	Patients	Does	ORR (%)	TCR (%)	OS (median)	PFS (median)
Uncontrolled tirals about gemcitabine-cisplatin combination							
Doval D 2004	India	GBC:30	G:1000 mg/m^2 C:70 mg/m^2(1)	11(36.67%)	18(60%)	20wks	18wks
Thongprasert S 2005	Thailand	GBC:1 CC:39	G:1250 mg/m^2 C:75 mg/m^2(1)	11(27.50%)	24(60.00%)	36wks	20.6wks
Park B 2006	Korea	GBC:13 CC:14	G:1000 mg/m^2 C:75 mg/m^2(2)	9(33.33%)	16(59.26%)	10mths	5.6mths
Lee G 2006	Korea	CC:24	G:1000 mg/m^2 C:70 mg/m^2(1)	5(20.83%)	17(70.83%)	9.3mths	4.98mths
Kim S 2006	Korea	GBC:10 CC:18 Ampulla: 1	G:1250 mg/m^2 C:60 mg/m^2(1)	10(34.48%)	14(48.28%)	11mths	3mths
Giuliani F 2006	Italy	GBC: 10 CC: 28	G:1000 mg/m^2 C:75–80 mg/m^2(1)	12(31.58%)	20(52.63%)	8mths	4mths
Charoentum C 2007	Thailand	CC:42	G: 1250 mg/m^2 C:75 mg/m^2 (1)	9(21.43%)	20(47.62%)	10.8mths	8.5mths
Meyerhardt J 2008	USA	GBC:5 CC:28	G:1000 mg/m^2 C:30 mg/m^2 (3)	7(21.21%)	19(57.58%)	9.7mths	6.3mths
Lee J 2008	South Korea	GBC:14 CC:20 Ampulla: 1	G:1250 mg/m^2 C:70 mg/m^2(3)	CC:4(11.43%) Others: 2 (5.71%)	CC:6 (17.14%) Others: 10 (28.57%)	8.6mths	3.2mths
Sasaki T 2010	Japan	GBC:5 CC:14 Ampulla:1	G:1000 mg/m^2 C:25 mg/m^2 (3)	0(0.00%)	14(70.00%)	6.75mths	3.4mths
Goldstein D 2010	Australia, New Zealand	GBC:22 CC:25 Ampulla:2 Unknown:1	G:1000 mg/m^2 C:20 mg/m^2 iv(3)	13(26.00%)	25(50.00%)	6.8mths	4mths
Uncontrolled studies about gemcitabine							
Mezger J 1998	Germany	GBC:4 CC:9	G:1000 mg/m^2 (4)	1(7.7%)	1(7.7%)	-	7 mths
Valencak J 1999	Germany	GBC:13 CC:25	G:1200 mg/m^2 (5) G:2200 mg/m^2 (5)	4(16.67%) 4(28.57%)	12(50%) 9(64.29%)	6.8mths 10.5mths	3.5mths 4.8mths
Gallardo J 2001	Chile	GBC:26	G:1000 mg/m^2(6)	9(34.62%)	15(57.69%)	30wks	-
Penz M 2001	Austria	GBC:10 CC:22	G:2200 mg/m^2 biweekly	7(21.88%)	21(65.63%)	11.5mths	5.6mths
Lin MH 2003	China	GBC:4 CC:16 Ampulla: 4	G:1000 mg/m^2 (6)	3(12.50%)	11(45.83%)	6.775mths	3.025mths
Eng C 2004	USA	GBC:9 CC:6	G:1500 mg/m^2(7)	0(0.00%)	2(13.33%)	22wks	11wks
Tsavaris N 2004	Greece	GBC:14 CC:14 Ampulla: 2	G:800 mg/m^2 weekly	9(30.00%)	20(66.67%)	14mths	7mths
Park J 2005	Korea	GBC:8 CC:15	G:1000 mg/m^2 (8)	6(26.09%)	14(60.87%)	13.12mths	8.1mths
von Delius S 2005	Germany	GBC:3 CC:16	G:1000 mg/m^2(7)	1(5.26%)	11(57.89%)	7.5mths	3.6mths
Okusaka T 2006	Japan	GBC:22 CC:12 Ampulla: 6	G:1000 mg/m^2(9)	7(17.50%)	22(55.00%)	7.6mths	2.6mths
RCTs							
Okusaka T 2010	Japan	GC:GBC:15 CC:22 Ampulla: 4 G:GBC:15 CC:22 Ampulla: 4	G: 1000 mg/m^2, d1, 8, 15, q28d; GC: G 1000mg/m^2 +C 25 mg/m^2, d1, 8, q21d	GC:8(19.5%) G:5(11.9%)	GC:28(68.3%) G:21(50%)	GC:11.2mths G:7.7mths	GC:5.8mths G:3.7mths
Valle J 2010	UK	GC:GBC:76 CC:119 Ampulla: 11 G:GBC:73 CC:122 Ampulla: 9		GC:59.3% G:42.5%	GC:131(81.4%) G:102(71.8%)	GC:11.7mths G:8.1mths	GC:8.0mths G:5.0mths

G, gemcitabine; C, cisplatin; GC, gemcitabine + cisplatin; (1) G, i.v., on d1, 8; C, i.v., on d1; every 3 Wks; (2) G, i.v. on d1, 8, 15; C, i.v. on d1; every 4 Wks; (3) G, i.v. on d1, 8; C, i.v., on d1, 8; every 3 Wks; (4) G, weekly for 7 weeks, 1 week rest, then cycles of 3-week treatments separated by an interval of 1 week; (5) G, days 1, 8, and 15 with 2 weeks rest; (6) G, i.v. weekly, every 3 Wks, 1 Wks rest; (7) G, i.v. weekly, every 3 Wks; (8) G, i.v. weekly; every 2 Wks, 1 Wks rest; (9) G, days 1, 8, and 15 for every 28 days; BTC, biliary tract carcinomas; GBC, gallbladder carcinoma; CC, cholangiocarcinoma; ORR, overall response rate; TCR, tumour control rate; OS, overall survival; PFS: progression-free survival

Table 2. Methodological Quality of the Two RCTs

Study	Randomization	Concealed allocation	Selective reporting	Incomplete outcome data	ITT analysis	Other biases
Okusaka T 201040	Mentioned	Unclear	No	No	No	Unclear
Valle J 201041	Yes	Yes	No	No	Yes	No

Tsavaris et al., 2004; Park et al., 2005; Thongprasert et al., 2005; Von et al., 2005; Giuliani et al., 2006; Kim et al., 2006; Lee et al., 2006; Okusaka et al., 2006; Park et al., 2006; Charoentum et al., 2007; Lee et al., 2008; Meyerhardt et al., 2008; Okusaka et al., 2010; Sasaki et al., 2010; Valle et al., 2010; Goldstein et al., 2011) were selected for the purposes of this study (Figure 1).

Uncontrolled trials about gemcitabine-cisplatin combination

There were 11 phase II studies (Doval et al., 2004; Park et al., 2005; Thongprasert et al., 2005; Giuliani et al., 2006; Kim et al., 2006; Lee et al., 2006; Charoentum et al., 2007; Lee et al., 2008; Meyerhard et al., 2008; Sasaki et al., 2010; Goldstein et al., 2011) of gemcitabine-cisplatin combination for advanced BTC. The number of patients ranged from 20 to 50. Study characteristics are presented in Table 1. Three quarters (Doval et al., 2004; Park et al., 2005; Thongprasert et al., 2005; Kim et al., 2006; Lee et al., 2006; Charoentum et al., 2007; Lee et al., 2008; Sasaki et al., 2010) of the included articles were conducted in Asia. Baseline characteristics of participants were different: one trial ((Doval et al., 2004) only recruited patients with GBC, and two (Lee et al., 2006; Charoentum et al., 2007) only included patients with CC, while others recruited patients with GBC, or CC, or ampullary tumor. Of all the trials, only one (Lee et al., 2008) reported their therapeutic results based on the different types of the carcinomas, so we cannot evaluate the efficacy and safety according to the disease location.

Of the 368 patients, 93 ORR responders were observed resulting in a pooled ORR of 25.27% (95%CI 21.11% 29.97%), and 203 TCR responders were observed resulting in a pooled TCR of 55.16% (95%CI 50.05% 60.16%). The mean PFS and OS for all patients were 4.86 months and 8.63 months, respectively.

Grade 3 or higher adverse events were observed in the use of gemcitabine-cisplatin combination: anemia (74/333), febrile neutropenia (7/112), neutropenia (79/276), thrombocytopenia (42/304), leucopenia (19/101), hemorrhage (2/80), nausea (10/112), vomiting (8/83), fatigue (11/83), diarrhea (2/74), granulocytopenia (10/30), cardiac infarction (1/50), anorexia (2/50), hepatic impairment (3/30), renal impairment (2/30), and neuropathy (1/33).

Uncontrolled trials about gemcitabine alone

There were 10 phase II studies (Metzger et al., 1998; Valencak et al., 2000; Gallardo et al., 2001; Penz et al., 2001; Lin et al., 2003; Eng et al., 2004; Tsavaris et al., 2004; Park et al., 2005; Von et al., 2005; Okusaka et al., 2006) of gemcitabine for advanced BTC and the number of patients ranged from 14 to 40. Study characteristics are presented in Table 1. Unlike that most of the uncontrolled trials of gemcitabine-cisplatin combination were conducted in Asia, only three uncontrolled trials (Lin et al., 2003; Park et al., 2005; Okusaka et al., 2006) of gemcitabine were performed in Asia. The other trials were conducted in either Europe or Americas. Gemcitabine was given 1000 mg/m^2 in more than half of the trials, but the exact regimes were different in these trials. Among all the 260 patients with advanced carcinoma, 113 patients were confirmed GBC, 135 had confirmed carcinomas of bile duct and 12 patients had ampullary carcinomas. None of the trials reported their results based on the different types of the cancers, which prevented us from assessing the efficacy according to the types of the carcinoma.

Of the 260 patients, 51 ORR responders were observed resulting in a pooled ORR of 19.62% (95%CI 14.79% 24.45%), and 138 TCR responders were observed resulting in a pooled TCR of 53.08% (95%CI 47.01% 59.15%). Further, the mean PFS and mean OS for all patients were 4.72 months and 8.79 months, respectively. The following grade 3 or higher adverse events were reported in these studies: neutropenia (26/153), leucopenia (17/119), thrombocytopenia (20/162), anemia (14/159), febrile neutropenia (1/15), infection (4/65), granulocytopenia (7/68), fatigue (3/39), nausea (3/55), vomiting (4/64), anorexia (5/70), diarrhea (2/15), constipation (3/40).

RCTs about gemcitabine-cisplatin combination versus gemcitabine

Characteristics of the RCTs: Two studies (Okusaka et al., 2010; Valle et al., 2010) (493 patients) comparing gemcitabine-cisplatin combination with gemcitabine for patients with advanced BTC were included (Table 1). They were both multi-centre trials. One trial (Okusaka et al., 2010) (84 patients) was performed in Japan, and the other (Valle et al., 2010) (410 patients) was conducted in Britain. These two trials adopted the same chemotherapy regimen: gemcitabine 1000 mg/m^2 on days 1, 8 and 15 of a 28-day cycle for one group, while cisplatin 25 mg/m^2 followed by gemcitabine 1000 mg/m^{2}on days 1, 8 of a 21-day cycle were used in the other group, but the maximum therapy periods were not the same (48 weeks, Okusaka et al., 2010; 24 weeks, Valle et al., 2010).

Methodological quality of the two RCTs: Six items (randomization, concealled allocation, selective reporting, incomplete outcome data, intention to treatment analysis, other biases) important for avoiding bias of the effect estimation were used to assess the methodological quality of the two trials. Considering the fact that gemcitabine alone was administered as a 30-minute infusion on days 1, 8 and 15 of a 28-day cycle, and cisplatin-gemcitabine combination were given as two-hour infusions on days 1 and 8 of a 21-day cycle, the different non-treatment weeks in each cycle unblinded the clinicians, so binding was not assessed in this article. Detailed methodological quality is provided in Table 2.

Efficacy and the evidence level of the results

The pooled results revealed that the mean OS for patients in the gemcitabine-cisplatin group was significantly longer than in the gemcitabine group (mean difference [MD] 3.59, 95% CI 3.48 3.71) with no heterogeneity (I^2=0%, P<0.00001). The mean PFS in the gemcitabine-cisplatin group seemed longer than that in the gemcitabine group (MD 2.57, 95%CI 1.69 3.45), but a high heterogeneity (I^2=95%, P<0.00001) existed. Significant differences in ORR (RR 1.59, 95%CI 1.04 2.43) and TCR (RR 1.15, 95%CI 1.02 1.31) (Okusaka et al., 2010; Valle et al., 2010) were seen without statistical heterogeneities.

Though the four outcomes all showed that gemcitabine-cisplatin had greater efficacy than gemcitabine for BTC, but the evidence level was different. The outcome of OS achieved moderate evidence level, which indicates that further research is likely to have an important impact on the confidence in the estimate of effect and might change the estimate. The remaining three outcomes (ORR, PFS, TCR) we evaluated were all with low evidence level, which indicates that further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.

Safety and the evidence level of the results

These two studies (Okusaka et al., 2010; Valle et al., 2010) both reported hematological and non-haematological adverse events. Hematological events included leucopenia, anemia, neutropenia, and thrombocytopenia. Statistically significant differences were seen for anaemia (RR 2.29, 95%CI 1.26 4.18) and neutropenia (RR 1.52, 95%CI 1.07 2.17), but not for leucopenia (RR 1.41, 95%CI 0.92 2.16) and thrombocytopenia (RR 2.45, 95%CI 0.62 9.70). However, no statistically significant differences were found for non-haematological adverse events, including nausea (RR 1.15, 95%CI 0.42 3.11), vomiting (RR 0.91, 95%CI 0.40 2.10), diarrhea (RR 1.91, 95%CI 0.69 5.28), anorexia (RR 0.65, 95%CI 0.20 2.13), lethargy (RR 1.10, 95%CI 0.72 1.68), constipation (RR 0.75, 95%CI 0.17 3.32), renal impairment (RR 2.20, 95%CI 0.50 9.73), ALT increase (RR 0.82, 95%CI 0.31 2.14), AST increase (RR 0.77, 95%CI 0.46 1.29), and elevated bilirubin level (RR 0.45, 95%CI 0.09 2.32).

We also assessed the evidence level of anaemia and neutropenia, which were thought to happen more in the combination group than the gemcitabine group. But we found the results were with low level and further studies are likely to change the current conclusions.

Discussion

In this study, we systematically evaluated the efficacy and adverse events of gemcitabine and gemcitabine-cisplatin combination for advanced BTC, and assessed the evidence level of the results concluded from RCTs. The data from phase II trials indicated that gemcitabine, either alone or in combination with cisplatin, might have clinical activity and responses for advanced BTC. Results of the two RCTs revealed that gemcitabine-cisplatin combination versus gemcitabine alone, increased OS, prolonged mean PFS, and produced significant increases in ORR and TCR, with generally acceptable grade 3 or 4 adverse events for patients with advanced BTC. Most adverse events related to the treatments were common in the two groups, including hematological adverse events (leucopenia, anemia, neutropenia, and thrombocytopenia) and non-hematological adverse events (nausea, vomiting, diarrhea, anorexia, fatigue, constipation, renal impairment). Only two of them (anaemia, neutropenia) were higher in the combination group than in the monotherapy group. Fortunately, they were both manageable and well-tolerated. As for the evidence levels of the efficacy and adverse events, only one achieved moderate evidence level, and others were all with low level. Gemcitabine is a potent cytotoxic agent, which incorporates gemcitabine triphosphate into DNA and inhibits replication with the subsequent induction of apoptosis (Pasetto et al., 2007). The efficacy of gemcitabine was reported related with the expression of ribonucleotide reductase M1 (RRM1), a subunit of the enzyme ribonucleotide reductase and a key molecule for gemcitabine resistance. In lung cancer, its expression is predictive of shorter survival treated by gemcitabine and platinum (Wang et al., 2011), and the gemcitabine-chemotherapy treatments have been established according to the RRM1 status. However, the same standards have not been established in BTC treatment. Studies revealed that the treatment efficacy was also related with multi-drug resistance-associated protein 3 (MRP3), which contributed to the intrinsic multi-drug resistance of the gemcitabine and its expression indicating bad efficacy of the chemotherapy (Rau et al., 2008). Cisplatin acts synergistically with gemcitabine, and the addition of cisplatin produces additional benefits.

BTC are a diverse collection of cancers and conflicting opinions existed about the responses to anti-cancer treatments for different types. Patients with GBC were reported to have better survival expectations than those with CC when treated with the same regimen in several trials (Gallardo et al., 2001; Penz et al., 2001; Tsavaris et al., 2004; Park et al., 2005), but one RCT (Valle et al., 2010) found no difference in response rate between the GBC and CC subgroups. The pooled analysis by Eckel (Rau et al., 2008) showed a higher response rate to chemotherapy, but shorter OS for patients with GBC than those with other types of BTC. We intended to evaluate the efficacy and safety of the chemotherapy according to the location of the carcinomas, but after screening the full texts of the included trials, we found it impossible. Seldom trials reported their results based on the different locations of the carcinomas. A recently published study (Won et al., 2010) investigated anatomical site-related similarities and differences between GBC and CC, and also assessed the expression and clinical significance of functional proteins such as p53, survivin, thymidine phosphorylase, and excision repair cross complementing 1. They concluded that gallbladder and bile duct cancers were separate diseases with different clinicopathological characteristics and prognostic factors. GBC and CC should be a stratification factor for RCTs to conduct a subgroup analysis if adequate participants were recruited in future trials.

Though the baseline characteristics of the included uncontrolled trials about the combination and gemcitabine alone were different and the trials recruited patients with different kinds of carcinomas, the results except OS were all in favor of the gemcitabine-cisplatin combination. RCTs are considered the gold standard for evaluating the efficacy of clinical interventions and developing evidence based clinical practice guidelines, however they can yield biased results if their methodologies were less than rigorous or their published reports failed to report key items. So the methodological qualities of these two RCTs and the evidence levels of the outcomes are crucial for people to consider whether applying the intervention of gemcitabine-cisplatin combination to clinical as the standard treatment. Junji Furuse's study (Furuse et al., 2010) did a detailed comparison between efficacy and safety end-points between these two RCTs and thought gemcitabine- cisplatin could become an accepted standard treatment. After our rigor assessment of the evidence level, we found the condition disappointing. Many crucial aspects of the methodology were not reported and most important outcomes were with low evidence levels. Even though we still agree with the opinion that gemcitabine-cisplatin can be put into clinical as a standard treatment, caution should be exercised when attempting to adopt gemcitabine-cisplatin combination. At the same time, we should recognize the two RCTs respect the significant step forward in this field though the evidence level was not satisfactory. In the clinical views, BTC are rare tumors, accounting for less than 5% of cancers, and our literature search has revealed that the largest size of the phase II studies was 50 patients (gemcitabine-cisplatin) and 40 (gemcitabine alone). So the two RCTs (with 410 and 84 patients, respectively) represent a significant step forward in this field, and in some degree the numbers of patients in these two RCTs were "large". As a result, prospective studies need to be undertaken in international collaboration, which could make the number of patients larger and lead to the development of treatments that are truly beneficial for patients with advanced BTC.

In this study, all RCTs comparing gemcitabine-cisplatin with gemcitabine for advanced BTC and uncontrolled studies about gemcitabine-cisplatin or gemcitabine for advanced BTC were systematically searched. Methodological quality and evidence level were rigorously appraised with standardized evaluation instruments. However, there were still several limitations. Firstly, the methodological qualities of the two RCTs were low and the methodological qualities of the uncontrolled studies were not evaluated. Secondly, blinding could not be taken at present because gemcitabine alone was administered as a 30-minute infusion on days 1, 8 and 15 of a 28-day cycle while the cisplatin and gemcitabine combination were given as two-hour infusions on days 1 and 8 of a 21-day cycle. This resulted in different non-treatment weeks in each cycle, which un-blinded the clinicians and patients. None blinding may cause biased results either intentionally or unintentionally. In the future a solution to the "blinding" issue must be taken, such double simulation. Thirdly, the included studies had potential clinical heterogeneity. BTCs are categorized into different types based on different standards. For example, according to anatomic location BTC can be classified as either GBC or CC. Pathologically, GBC can be divided into four subtypes (adenocarcinoma, squamous cell and adenosquamous cell carcinoma, undifferentiated carcinoma, and rare tumors (Albores et al., 1992; Andrea et al., 2003), or two categories (squamous cell and non-squamous cell carcinomas (Andrea et al., 2003)). These tumors may differ with respect to biological behaviors, disease courses, and responsiveness to chemotherapy. In our included studies, different tumor types were included together and were not distinguished from each other when the results of efficacy were assessed, therefore no indication of the exact efficacy for each type of tumor were got. So stratification factors, such as disease sub-type, presence or absence of histological confirmation, should be considered and adjusted in light of future studies.

In conclusion: Available evidence showed that gemcitabine, either alone or in combination with cisplatin, had clinical activity and responses when used for the treatment of advanced BTC and gemcitabine-cisplatin gave rise to an improvement in OS, PFS, ORR, and TCR versus gemcitabine alone. The major toxicities associated with gemcitabine-cisplatin therapy were generally manageable and acceptable. Therefore, gemcitabine-cisplatin may be a valid option for patients with advanced BTC. However, the methodological qualities of RCTs were low, and most outcomes were considered to be low evidence level. In future, more and larger RCTs with multi-center (and multi-national) collaboration should be well designed to yield high quality data and different tumor entities should be segregated for analysis.

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