Original Article

The efficacy and safety of gemcitabine-based combination therapy *vs.* gemcitabine alone for the treatment of advanced pancreatic cancer: a systematic review and meta-analysis

Zhaohuan Zhang[1#], Shuling He[1#], Ping Wang[2], Yibing Zhou[3]

[1]Department of General Surgery, The First Affiliated Hospital of Jiamusi University, Jiamusi, China; [2]Criminal Technical Detachment, Jiamusi Public Security Bureau, Jiamusi, China; [3]Department of General Surgery, Jiamusi Central Hospital, Jiamusi, China

Contributions: (I) Conception and design: Z Zhang; (II) Administrative support: Y Zhou; (III) Provision of study materials or patients: Z Zhang, S He; (IV) Collection and assembly of data: S He, P Wang; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yibing Zhou. Department of General Surgery, Jiamusi Central Hospital, 256 Zhongshan Street, Xiangyang District, Jiamusi 154000, China. Email: 945860632@qq.com.

Background: Gemcitabine (GEM) is used as a standard first-line drug to effectively alleviate symptoms and prolong survival time for advanced pancreatic cancer. Most randomized controlled trials (RCTs) show that GEM-based combination therapy is better than GEM alone, while some RCTs have the opposite conclusion. This study aimed to investigate whether GEM-based combination therapy would be superior to GEM alone by a systematic review and meta-analysis.

Methods: According to the PICOS principles, RCTs (S) focused on comparing GEM-based combination therapy (I) *vs.* GEM alone (C) for advanced pancreatic cancer (P) were collected from eight electronic databases, outcome variables mainly include survival status and adverse events (AEs) (O). Review Manager 5.4 was used to evaluate the pooled effects of the results among selected articles. Pooled estimate of hazard ratio (HR) and odds ratio (OR) with 95% confidence interval (CI) were used as measures of effect sizes. Quality assessment for individual study was performed using the Cochrane tool for risk of bias.

Results: A total of 17 studies including 5,197 patients were selected in this analysis. The pooled results revealed that GEM-based combination therapy significantly improved the overall survival (OS; HR =0.84; 95% CI: 0.79 to 0.90; P<0.00001), progression-free survival (PFS; HR =0.78; 95% CI: 0.72 to 0.84; P<0.00001), overall response rate (ORR; OR =1.92; 95% CI: 1.61 to 2.30; P<0.00001), 1-year survival rate (OR =1.44; 95% CI: 1.02 to 2.03; P=0.04), respectively. Subgroup analysis showed that the efficacy of GEM plus capecitabine (CAP) and GEM plus S-1 was better than that of GEM alone, while GEM plus cisplatin (CIS) did not achieve an improved effect. GEM-based combination therapy can significantly increase the incidence of AEs, such as leukopenia (P<0.001), neutropenia (P<0.001), anemia (P<0.05), nausea (P<0.001), diarrhea (P<0.05), and stomatitis (P<0.001). No publication bias existed in our meta-analysis (P>0.10).

Discussion: Our study supported that GEM-based combination therapy was more beneficial to improve patient's survival than GEM alone, while there was no additional benefits in GEM plus CIS. We also found that GEM-based combination therapy increased the incidence of AEs. Clinicians need to choose the appropriate combination therapy according to the specific situation.

Keywords: Gemcitabine (GEM); capecitabine (CAP); S-1; cisplatin (CIS); pancreatic cancer

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Introduction

Pancreatic cancer is a malignant tumor with high mortality. Even with continued improvements in diagnostic technology, most patients with pancreatic cancer are often diagnosed at an unresectable, advanced stage (1,2). Currently, surgical resection is the only possible cure, but patients with advanced pancreatic cancer have usually missed their chance of surgery. The prognosis of patients with pancreatic cancer is often poor, the median survival time is only 3–6 months for patients with distant metastasis, and that of patients with local complications is only 6–10 months (3,4). Therefore, it is urgent to seek an effective chemotherapy regimen to improve the prognosis of pancreatic cancer.

Gemcitabine (GEM), a synthetic analog of cytarabine, whose structure is similar to that of deoxycytidine and cytarabine, is one of the most used chemotherapeutic drugs for pancreatic cancer (5,6). In 1997, GEM-based chemotherapy was first proposed as a standard therapy treatment for patients with unresectable pancreatic cancer. In recent decades, GEM has become a standard drug for chemotherapy of pancreatic cancer and a critical target drug for research (7,8). Most patients with advanced pancreatic cancer have symptoms such as severe pain, jaundice, weight loss, nausea, vomiting, and general weakness. Although the short-term objective efficacy of GEM for advanced pancreatic cancer is not obvious and the complete or partial remission rate is not high, at only 10–30%, research has found that GEM has a significant effect on the clinical benefit rate (CBR), such as the degree of pain, the dosage of painkillers, and weight gain, which greatly enhances the quality of life of patients with pancreatic cancer (9,10).

At the same time, in order to improve the therapeutic effect of pancreatic cancer treatment, since GEM entered the market, researchers have been trying to treat advanced pancreatic cancer based on GEM combined with many drugs, which has significantly improved the overall survival (OS) and progression-free survival (PFS) of patients (11-13). In particular, there have been many studies conducted on the combination of GEM with platinum- or fluorouracil-based drugs. Cisplatin (CIS) is the main platinum-based drug, and fluorouracil-based drugs include capecitabine (CAP) and S-1 (14,15). These 3 drugs have been shown to be effective in the treatment of pancreatic cancer. However, some studies have also shown that although the combined chemotherapy yielded a significant improvement in the overall response rate (ORR), some trials did not show a significant extension of OS (16,17). Some studies have also shown that 1-year survival rate, the median survival time, and CBR of combined chemotherapy were low, and the clinical treatment effect was not very satisfactory (18,19).

Most clinical randomized controlled trials (RCTs) have shown that GEM-based combination therapy is better than single drug treatment, while some RCTs have drawn the opposite conclusions (20-22). Therefore, there is no clear certainty whether GEM-based combination therapy is better than single drug chemotherapy. This article collects the efficacy and safety outcomes of GEM-based combination therapy *vs.* GEM alone for advanced pancreatic cancer, and conducted a systematic review and meta-analysis, in order to provide some guidance for clinical chemotherapy of advanced pancreatic cancer. We present the following article in accordance with the PRISMA reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-624/rc).

Methods

Literature search strategy

Eight databases were carefully searched from their inception to 1 April 2022 without limitations of language and publication status: PubMed, Cochrane Library, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese BioMedical Database (CBM), China Scientific Journal Database (VIP), and Wanfang Database. The following keywords were applied to search literature in combination with the Boolean operators 'AND' or 'OR': "gemcitabine", "capecitabine", "S-1", "cisplatin", and "pancreatic cancer". At present, GEM plus CAP, GEM plus S-1 and GEM plus CIS were the main combination therapies. To identify additional eligible studies, we reviewed reference lists from eligible trials and relevant reviews and guidelines. Any disagreements in the first or second phases were determined by discussion and consensus between the two reviewers.

Study selection

The inclusion criteria of the selected literatures were as follows: (I) patients with advanced pancreatic cancer; (II) research comparing patients receive GEM-based combination therapy *vs.* GEM alone; (III) studies were designed as RCT; (IV) researches on comparison of the efficacy and safety outcomes, such as OS, PFS, ORR, 1-year

survival rate, and adverse events (AEs).

Data extraction

We designed a data extraction form by consensus. One of the researchers performed all of the data extraction, and two investigators conducted independent verification. All of the above procedure were completed by two authors independently (Z Zhang, Shu He). The following contents were extracted from each article: first author's name, year of publication, study design, country, trial phase, intervention group, sample size, participant characteristics (gender, age), and the results of some outcome variables.

Quality assessment

The Cochrane Collaboration's risk of bias tool (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials) was used to assess the methodological quality of the selected studies, based on the following 7 items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. The total score of quality assessment was 8 points, which are scored by our two authors respectively. In case of disagreement, the final score was decided by the third author. We defined the score of 6–8 points as low risk ('good' quality), 3–5 points as unclear risk ('moderate' quality), and 0–2 points as high risk ('poor' quality).

Statistical analysis

Meta-analysis was conducted using the software Review Manager (RevMan 5.4, the Nordic Cochrane Centre, Copenhagen, Denmark). The outcome variables of this study included survival variables and dichotomous variables. The combined analysis of survival variables was presented by hazard ratio (HR) with 95% confidence interval (CI), and the pooled analysis of dichotomous variables was expressed by odds ratio (OR) with 95% CI. The Cochran Q test and the Higgins I-squared (I^2) statistic were used for heterogeneity testing. When I^2>50% or P<0.10, a random effects model was used, otherwise a fixed effects model was used. We conducted the subgroup analysis according to the added drugs of combination therapy. The funnel plot and Egger's test were performed to detect the publication bias. P value was used to detect the statistical difference, which was statistically significant when P<0.05.

Results

Search process

A total of 1,678 potentially unique studies were identified. After removal of duplicates, a total of 1,465 records were remained. By reading the titles and abstracts, an additional 1,251 records were further excluded. Then, 197 articles were further excluded because of different study design or insufficient data available. A total of 17 studies were included in the final meta-analysis (20-36). The results of the search process were illustrated in a flowchart (*Figure 1*).

Characteristics of included studies

Table 1 listed the chief characteristics of the 17 selected trials. All the trials included were phase II or III. All of the control groups were GEM alone. In the intervention groups, 7 were the combination of GEM and CAP, 5 were the combination of GEM and S-1, and 5 were the combination of GEM and CIS. Totals of 2,370 and 2,827 patients were included in the test group and control group, respectively. The age of participants ranged from 27 to 85 years. The median time of OS and PFS in the test group and the control group of each article were shown in *Table 1*, where it can be seen that the median time of OS and PFS in the test group is greater than that in the control group.

Results of quality assessment

The quality of the selected studies were assessed in accordance with the Cochrane tool for risk of bias. Among the included studies, high risk of performance bias was detected in 7 articles and detection bias was found in 3 studies (*Figure 2*). *Figure 3* summarized the risk of bias for each included study.

Results of meta-analysis

OS

A total of 11 studies reported OS. The results of heterogeneity testing showed that there was insignificant heterogeneity among the included literature (I^2=7%; P=0.37), so the combined effect quantity was analyzed by the fixed effects model. The overall meta-analysis

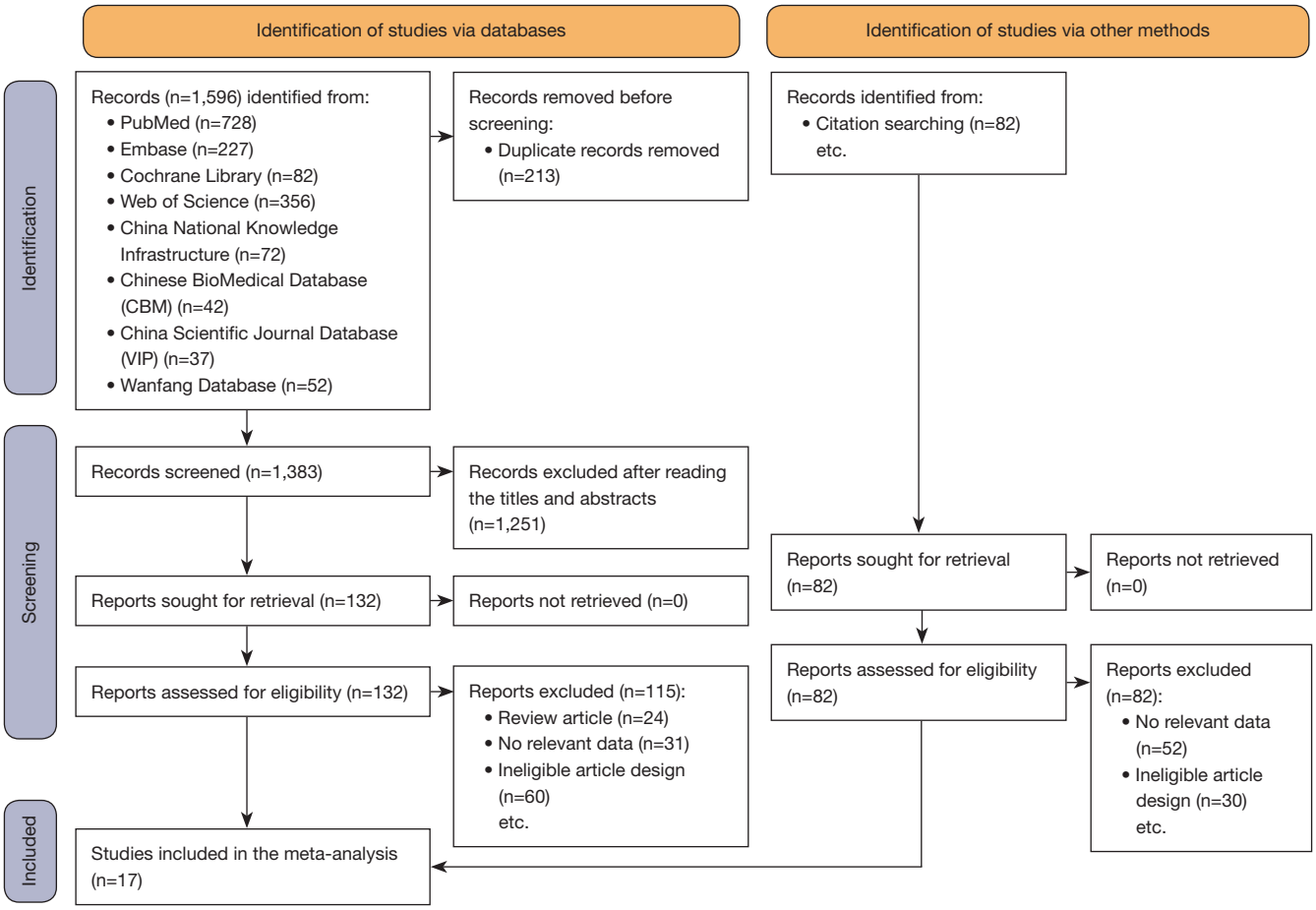

Figure 1 Flow diagram of literature search.

showed that HR =0.84 (95% CI: 0.79 to 0.90; P<0.00001), suggesting that GEM-based combination therapy can effectively improve OS (*Figure 4*). Subgroup analysis was carried out according to the added drugs and they were divided into a GEM plus CAP group, GEM plus S-1 group, and GEM plus CIS group. The subgroup analysis results showed that GEM plus CAP group and GEM plus S-1 group could effectively improve OS, and the HR values were 0.82 (95% CI: 0.75 to 0.90; P<0.0001), and 0.81 (95% CI: 0.71 to 0.94; P=0.004), respectively. Compared with GEM alone, GEM plus CIS group did not improve OS, and its HR was: 0.90 (95% CI: 0.79 to 1.02; P=0.09).

PFS

A total of 9 studies had data available for analysis of PFS. No significant heterogeneity was found among the included literature (I^2=34%; P=0.14). The overall meta-analysis results showed that HR was 0.78 (95% CI: 0.72 to 0.84; P<0.00001), indicating that GEM-based combination therapy can effectively improve PFS (*Figure 5*). The results of subgroup analysis showed that the GEM plus CAP group (HR =0.81, 95% CI: 0.72 to 0.90; P=0.0002) and the GEM plus S-1 group (HR =0.66, 95% CI: 0.57 to 0.76; P<0.00001) could effectively improve PFS, but GEM plus CIS group did not achieve an improvement, and its HR was 0.91 (95% CI: 0.77 to 1.09; P=0.31).

ORR

Thirteen trials evaluated ORR between GEM-based combination therapy and GEM alone. We used a fixed effect model as the moderate heterogeneity among the included literature (I^2=41%; P=0.06). The overall meta-analysis results showed that GEM-based combination therapy can effectively increase ORR (OR =1.92; 95% CI: 1.61 to 2.30; P<0.00001) (*Figure 6*). Subgroup analysis also showed that compared with GEM alone, both the

Table 1 Trial design and chief characteristics of the 17 studies included in the meta-analysis

Study	Country	Study design	Phase	Intervention		No. of patients		Gender (M/F)		Age (years), median [range]		OS (months)		PFS (months)	
				Test	Control	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control
Scheithauer, 2003	Austria	RCT	II	GEM + CAP	GEM	41	42	27/14	23/19	64 [40–75]	66 [39–75]	9.5	8.2	5.1	4.0
Herrmann, 2007	Germany	RCT	III	GEM + CAP	GEM	160	159	86/74	85/74	62 [27–83]	62 [36–84]	8.4	7.2	4.3	3.9
Bernhard, 2008	Germany	RCT	III	GEM + CAP	GEM	160	159	86/74	85/74	62 [27–83]	62 [36–84]	–	–	–	–
Cunningham, 2009	UK	RCT	III	GEM + CAP	GEM	267	266	160/107	153/113	62 [37–82]	62 [26–83]	7.1	6.2	5.3	3.8
Lee, 2017	Korea	RCT	III	GEM + CAP	GEM	108	106	63/45	57/49	64 [37–80]	64 [43–85]	10.3	7.5	6.2	5.3
Neoptolemos, 2017	UK	RCT	III	GEM + CAP	GEM	364	366	202/162	212/154	65 [39–81]	65 [37–80]	28.0	25.5	–	–
de Jong, 2022	Netherlands	RCT	III	GEM + CAP	GEM	164	614	78/86	342/272	66 [58–71]	67 [60–72]	31.4	22.1	–	–
Nakai, 2012	Japan	RCT	II	GEM + S-1	GEM	53	53	42/11	33/20	63 [40–82]	67 [42–84]	13.5	8.8	5.4	3.6
Ozaka, 2012	Japan	RCT	II	GEM + S-1	GEM	53	59	32/21	35/24	64 [45–77]	64 [41–79]	13.7	8.0	6.15	3.78
Sudo, 2013	Japan	RCT	II	GEM + S-1	GEM	51	50	27/24	34/16	66 [50–77]	67 [45–73]	8.6	8.6	5.3	3.8
Ueno, 2013	Japan	RCT	III	GEM + S-1	GEM	275	277	158/117	170/107	–	–	10.1	8.8	5.7	4.1
Imaoka, 2016	Japan	RCT	III	GEM + S-1	GEM	275	277	158/117	170/107	–	–	10.2	8.5	6.9	4.5
Colucci, 2002	Italy	RCT	III	GEM + CIS	GEM	53	54	35/18	27/27	60 [33–71]	63 [43–75]	2.5	1.7	1.7	0.7
Heinemann, 2006	Germany	RCT	III	GEM + CIS	GEM	98	97	64/34	60/37	64 [37–82]	66 [43–85]	7.5	6.0	5.3	3.1
Palmer, 2007	UK	RCT	II	GEM + CIS	GEM	26	24	13/13	13/11	66 [40–79]	66 [47–78]	15.6	9.9	–	–
Colucci, 2010	Italy	RCT	III	GEM + CIS	GEM	201	199	125/76	113/86	63 [35–75]	63 [37–75]	7.2	8.3	3.8	3.9
Chao, 2013	China	RCT	II	GEM + CIS	GEM	21	25	17/4	18/7	69 [47–81]	69 [46–83]	7.9	7.7	3.6	4.6

RCT, randomized controlled trial; GEM, gemcitabine; CAP, capecitabine; CIS, cisplatin; OS, overall survival; PFS, progression-free survival.

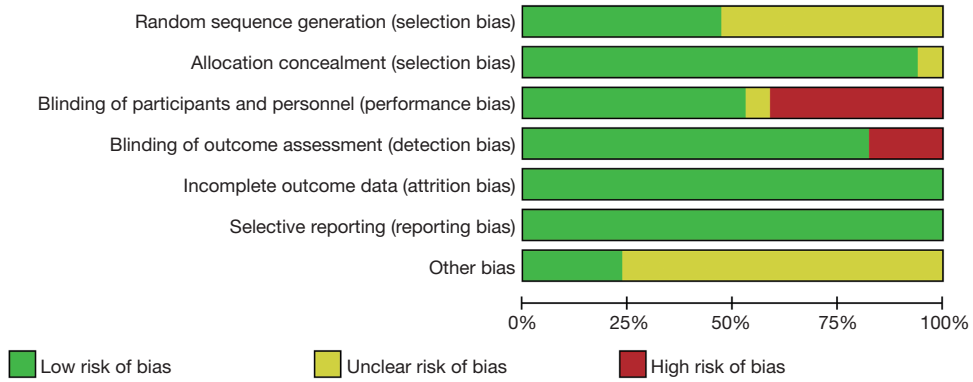

Figure 2 Risk of bias of all the included studies.

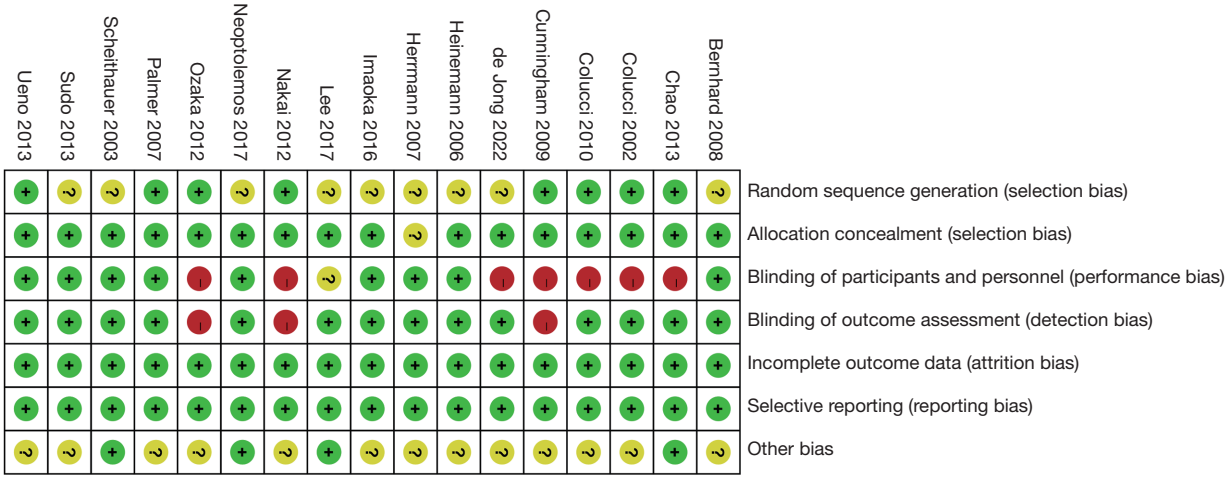

Figure 3 Risk of bias summary for each included study.

GEM plus CAP group (OR =1.61; 95% CI: 1.22 to 2.13; P=0.0009) and the GEM plus S-1 group (OR =2.65; 95% CI: 1.99 to 3.52; P<0.00001) could significantly improve ORR, but the GEM plus CIS group (OR =1.40; 95% CI: 0.93 to 2.11; P=0.11) did not achieve same effect.

One-year survival rate

A total of 9 studies containing 2,077 patients reported the 1-year survival rate. We used the random effects model due to the significant heterogeneity (I^2=58%; P=0.01). Although the overall meta-analysis showed that GEM-based combination therapy could significantly increase 1-year survival rate (OR =1.44; 95% CI: 1.02 to 2.03; P=0.04) (*Figure* 7), the subgroup analysis showed that compared with GEM alone, only the GEM plus S-1 Group (OR =2.32; 95% CI: 1.37 to 3.92; P=0.002) could significantly increase 1-year survival rate, but the GEM plus CAP Group (OR =1.06; 95% CI: 0.73 to 1.53; P=0.77) and GEM plus CIS group (OR =0.99; 95% CI: 0.70 to 1.42; P=0.97) did not.

AEs

The pooled AEs (grade ≥3) were summarized in *Table 2*. The AEs mainly included hematological toxicity and non-hematological toxicity. Common hematological toxicity included leukopenia, neutropenia, thrombocytopenia, and anemia; non-hematological toxicity included nausea, vomiting, diarrhea, constipation, anorexia, and stomatitis. As compared with GEM alone, GEM-based combination therapy had a significantly higher incidence of leukopenia (OR =2.25; 95% CI: 1.67 to 3.01; P<0.00001), neutropenia (OR =1.93; 95% CI: 1.61 to 2.32; P<0.00001), anemia (OR =1.40; 95% CI: 1.05 to 1.86; P=0.02), nausea/

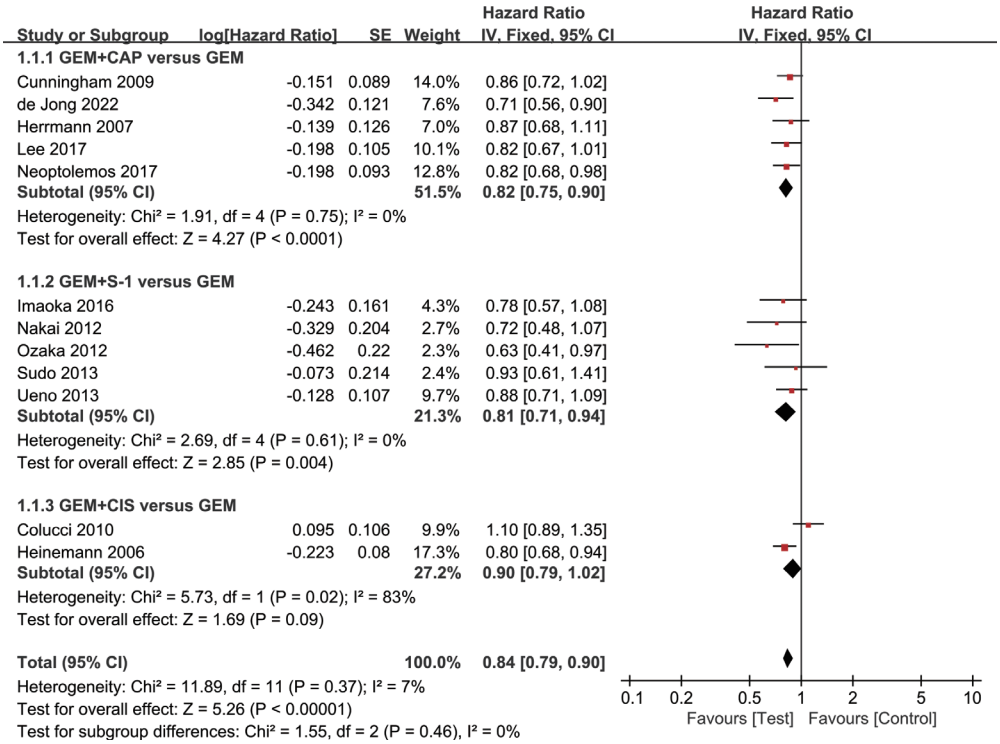

Figure 4 Forest plot showing the HR in the OS between test groups and control groups. SE, standard error; CI, confidence interval; GEM, gemcitabine; CAP, capecitabine; CIS, cisplatin; HR, hazard ratio; OS, overall survival.

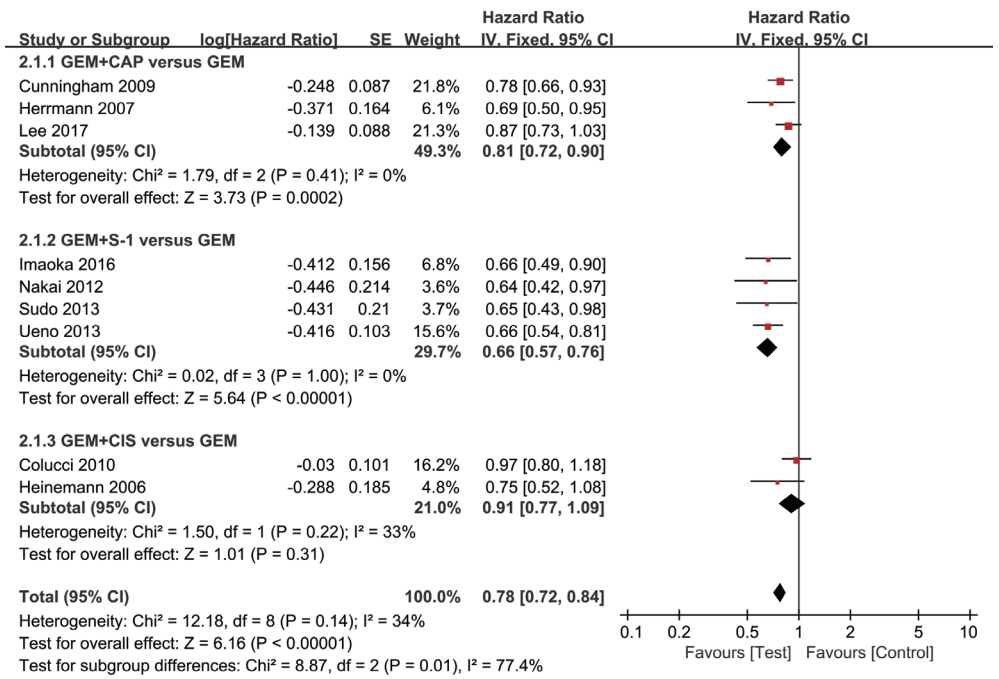

Figure 5 Forest plot showing the HR in the PFS between test groups and control groups. SE, standard error; CI, confidence interval; GEM, gemcitabine; CAP, capecitabine; CIS, cisplatin; HR, hazard ratio; PFS, progression-free survival.

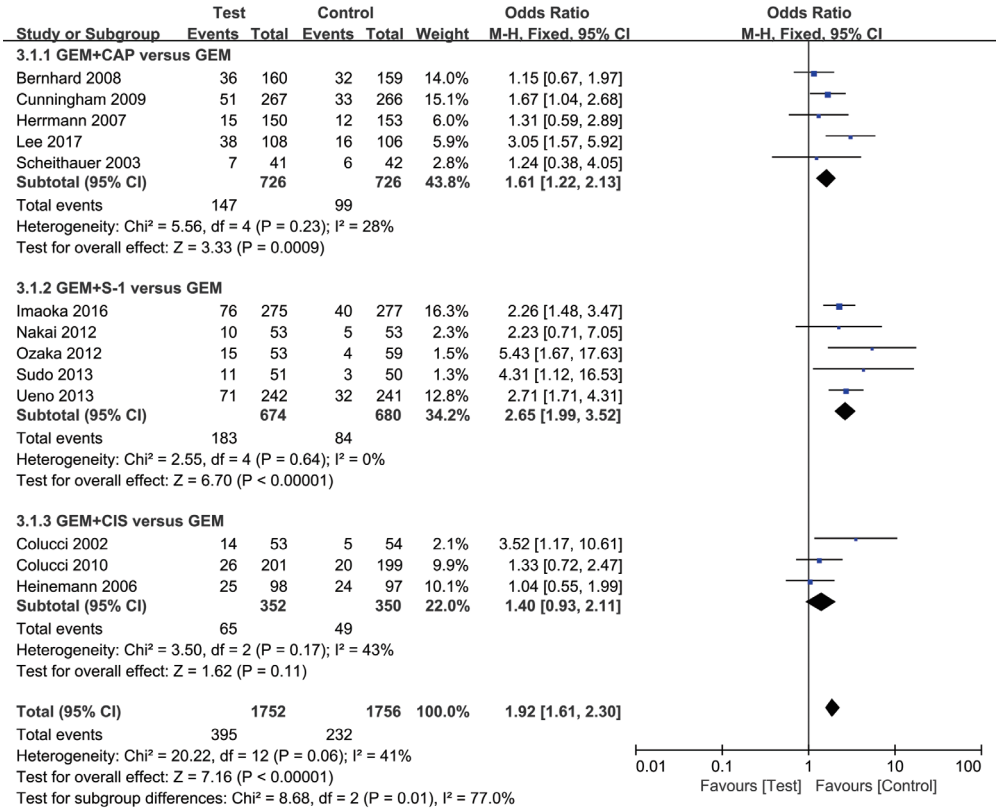

Figure 6 Forest plot showing the OR in the ORR between test groups and control groups. CI, confidence interval; GEM, gemcitabine; CAP, capecitabine; CIS, cisplatin; OR, odds ratio; ORR, overall response rate.

vomiting (OR =1.97; 95% CI: 1.43 to 2.72; P<0.0001), diarrhea/constipation (OR =1.68; 95% CI: 1.08 to 2.62; P=0.02), and stomatitis (OR =4.44; 95% CI: 2.00 to 9.87; P=0.003), yet there was no difference in the incidence of thrombocytopenia (OR =1.26; 95% CI: 0.96 to 1.64; P=0.09) and anorexia (OR =1.17; 95% CI: 0.73 to 1.89; P=0.51).

Publication bias

Funnel plot analysis and Egger' test for the outcomes of OS, PFS, ORR, and 1-year survival rate were performed to explore the publication bias. The plots showed no obvious asymmetry, and the P value of Egger' test for all outcomes were more than 0.10, suggesting that no publication bias existed (*Figure 8*).

Discussion

Pancreatic cancer is a common malignant tumor in the digestive system. Due to its occult onset, rapid development, and high degree of malignancy, although the diagnosis of pancreatic cancer has been improved compared with the previous diagnosis, it remains difficult to diagnose and it is still inevitable that patients will be diagnosed in the advanced stage (37,38). Most pancreatic cancer patients are in advanced stage or have distant metastasis at the time of seeing a doctor and have lost the opportunity for surgery. The treatment of these patients can only be palliative, based on chemotherapy to improve the quality of life and survival time of patients. The cytosine nucleoside derivative, GEM, is an antimetabolic and antitumor drug. It is a water-soluble analog of deoxycytidine, which can inhibit cell replication and ribonucleotide reductase, thus inhibiting DNA synthesis and repair (39). It has a good therapeutic effect on pancreatic cancer. Since the clinical trial in 1992, GEM has been the basic drug for chemotherapeutic treatment of pancreatic cancer, especially for patients who cannot undergo surgery, with certain benefits (40). However, due to the limited clinical benefits of GEM and substantial toxic and side effects, including bone marrow suppression, toxic

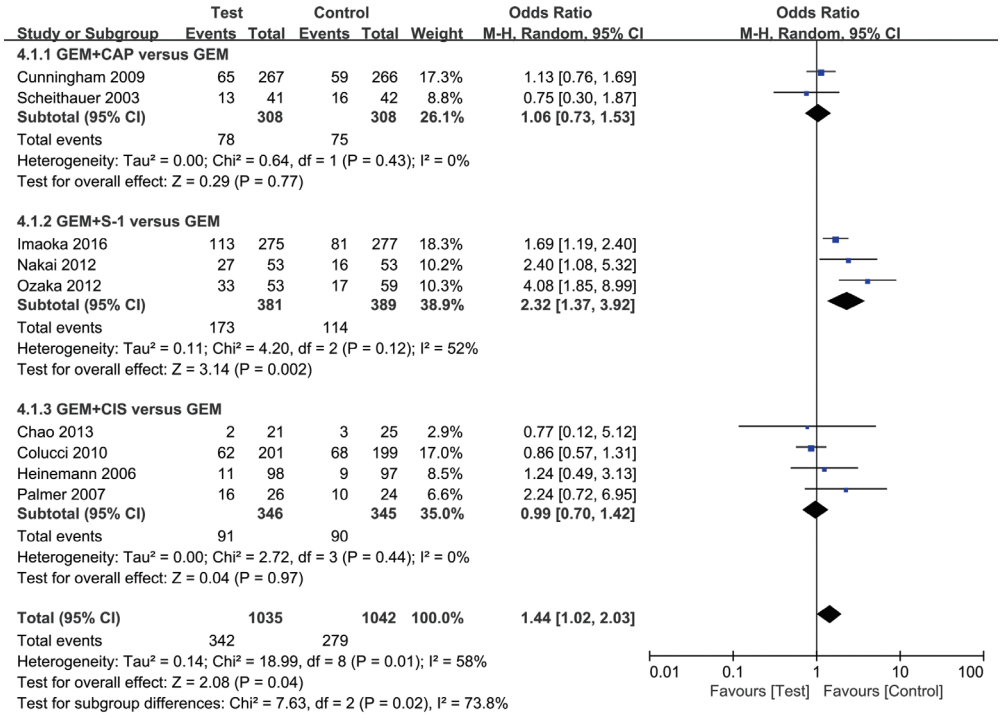

Figure 7 Forest plot showing the OR in the 1-year survival rate between test groups and control groups. CI, confidence interval; GEM, gemcitabine; CAP, capecitabine; CIS, cisplatin; OR, odds ratio.

and side effects of digestive system, hepatorenal toxicity, and allergic reaction, it is very challenging for both patients and clinicians. Therefore, GEM-based treatment combined with other drugs is proposed for use in the clinic (41,42).

This study conducted multiple searches within multiple medical databases, and screened them in strict accordance with the pre-established inclusion criteria. The evaluation of literature quality requires that there is no great risk of bias, so the original studies included in the analysis were high-quality clinical studies. The funnel plots were basically symmetrical and evenly dispersed, suggesting that the possibility of publication bias was small. Therefore, this study had high reliability. A meta-analysis of 5,197 patients from 17 RCTs showed that GEM-based combination therapy improved OS and PFS, which had obvious survival advantages, and the ORR and 1-year survival rate were also higher than those of GEM alone. It showed obvious survival benefits, which supported that GEM-based combination therapy can effectively alleviate the disease progression and prolong the life of patients. However, subgroup analysis showed that GEM plus CAP and GEM plus S-1 could effectively improve OS, PFS, and ORR, but GEM plus CIS did not achieve the same effect. Li *et al.*'s meta-analysis compared the effects of GEM plus fluorouracil-based drugs (CAP and S-1) with GEM alone in advanced pancreatic cancer, and they concluded that compared with GEM alone, GEM combined with fluorouracil significantly improved OS and increased 1-year survival and ORR in patients with advanced pancreatic cancer (43). Zhou *et al.*'s meta-analysis compared the effects of GEM plus CIS and GEM alone in advanced pancreatic cancer. Their results showed that GEM plus CIS could benefit patients in ORR, but could not make patients obtain better clinical efficacy and long-term prognosis than GEM alone (44). Our study was consistent with the conclusions of the above two studies.

In terms of drug toxicity and side effects, our study showed that GEM-based combination therapy increased various toxic and side effects, mainly in the hematological system and digestive system. However, its incidence was not high, and these toxic and side effects can be predicted and controlled (45,46). Platinum- and fluorouracil-based drugs have great cytotoxicity, so they were found unsuitable for elderly patients with late pancreatic cancer treatment and poor physical fitness. Therefore, GEM plus CIS only had potential benefits in patients with better physical fitness. Studies have shown that fluorouracil drugs had better

Table 2 The difference of AEs (grade ≥3) between test group and control group

AEs	Subgroup	Studies	Subgroup OR (95% CI)	Subgroup P value	Pooled OR (95% CI)	Pooled P value
Hematological						
Leukopenia	GEM + CAP *vs.* GEM	1	1.33 (0.28, 6.39)	0.720	2.25 (1.67, 3.01)	<0.00001
	GEM + S-1 *vs.* GEM	3	2.62 (1.85, 3.71)	<0.00001		
	GEM + CIS *vs.* GEM	4	1.56 (0.87, 2.81)	0.130		
Neutropenia	GEM + CAP *vs.* GEM	4	1.61 (1.20, 2.16)	0.001	1.93 (1.61, 2.32)	<0.00001
	GEM + S-1 *vs.* GEM	4	2.34 (1.77, 3.09)	<0.00001		
	GEM + CIS *vs.* GEM	4	1.83 (1.19, 2.80)	0.006		
Thrombocytopenia	GEM + CAP *vs.* GEM	4	0.45 (0.27, 0.76)	0.003	1.26 (0.96, 1.64)	0.090
	GEM + S-1 *vs.* GEM	4	2.03 (1.33, 3.11)	0.001		
	GEM + CIS *vs.* GEM	4	1.86 (1.09, 3.20)	0.020		
Anemia	GEM + CAP *vs.* GEM	4	1.43 (0.83, 2.45)	0.200	1.40 (1.05, 1.86)	0.020
	GEM + S-1 *vs.* GEM	4	1.26 (0.85, 1.87)	0.240		
	GEM + CIS *vs.* GEM	4	1.78 (0.93, 3.40)	0.080		
Non-hematological						
Nausea/vomiting	GEM + CAP *vs.* GEM	4	1.24 (0.79, 1.93)	0.350	1.97 (1.43, 2.72)	<0.0001
	GEM + S-1 *vs.* GEM	4	3.12 (1.57, 6.20)	0.001		
	GEM + CIS *vs.* GEM	4	3.44 (1.70, 6.95)	0.0006		
Diarrhea/ constipation	GEM + CAP *vs.* GEM	4	1.67 (0.87, 3.21)	0.120	1.68 (1.08, 2.62)	0.020
	GEM + S-1 *vs.* GEM	4	2.95 (1.20, 7.28)	0.020		
	GEM + CIS *vs.* GEM	4	0.92 (0.38, 2.23)	0.850		
Anorexia	GEM + CAP *vs.* GEM	NR	–	–	1.17 (0.73, 1.89)	0.510
	GEM + S-1 *vs.* GEM	4	1.08 (0.66, 1.77)	<0.001		
	GEM + CIS *vs.* GEM	1	4.02 (0.45, 36.29)	0.220		
Stomatitis	GEM + CAP *vs.* GEM	3	4.02 (1.13, 14.33)	0.030	4.44 (2.00, 9.87)	0.0003
	GEM + S-1 *vs.* GEM	4	7.41 (1.67, 32.86)	0.008		
	GEM + CIS *vs.* GEM	2	2.63 (0.60, 11.50)	0.200		

AEs, adverse events; GEM, gemcitabine; CAP, capecitabine; CIS, cisplatin; NR, not reported; OR, odds ratio; CI, confidence interval.

biological selectivity, tolerance, and lower toxicity and side effects than platinum drugs, and can be used in patients who are not suitable for combination therapy with platinum or other drugs (47,48).

It has been found that GEM also has toxic and side effects of bone marrow suppression. Due to the limited efficacy of GEM alone and the emergence of toxic and side effects and drug resistance of high-dose use, many researchers continue to explore the combination of drugs in the treatment of cancer (49). Most researchers believe that two or more synergistic anticancer drugs can reduce the toxicity and side effects of single drug use and reduce the generation of single drug resistance to a certain extent, improve the metabolic dynamics of drugs *in vivo*, improve the therapeutic effect of drugs, and reduce the side effects of drugs. Shi *et al.* retrospectively evaluated the clinical effect of arterial infusion of GEM hydrochloride and fluorouracil drugs for advanced pancreatic cancer, and found that it can obtain better clinical benefits and improve the survival time of patients (50). Shu *et al.* compared the toxicity and side

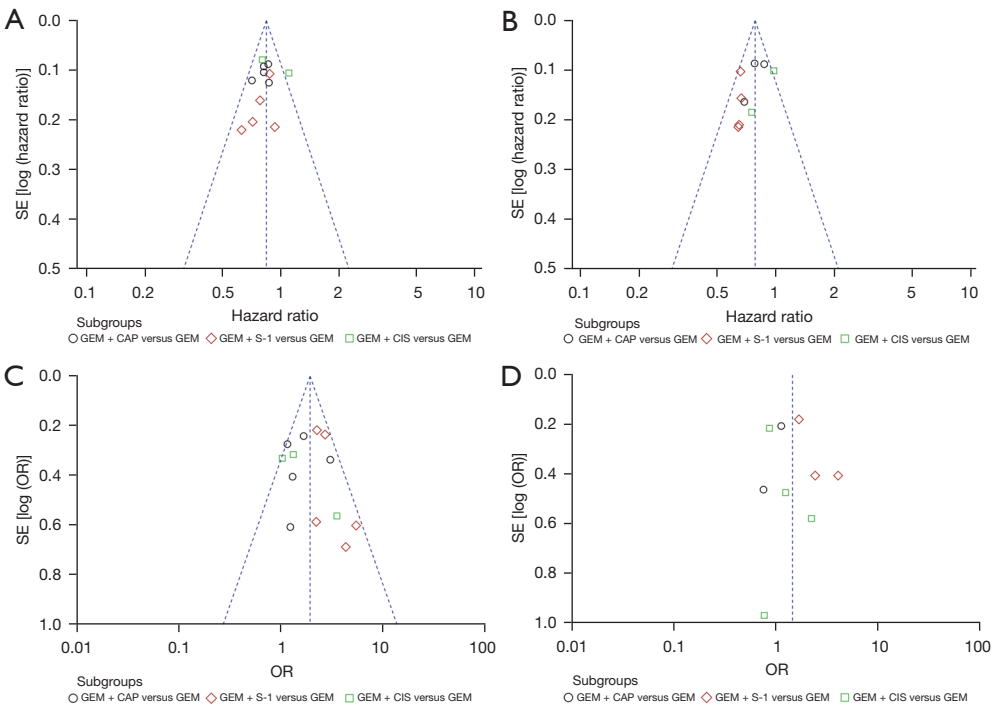

Figure 8 Funnel plots to detect publication bias. (A) OS; (B) PFS; (C) ORR; (D) 1-year survival rate. SE, standard error; GEM, gemcitabine; CAP, capecitabine; CIS, cisplatin; OR, odds ratio; OS, overall survival; PFS, progression-free survival; ORR, overall response rate.

effects and short-term efficacy of GEM hydrochloride plus fluorouracil and GEM hydrochloride plus CIS for advanced pancreatic cancer. The results showed that the former had a higher clinical benefit response rate and no significant difference in side effects (51).

In clinical practice research, we continuously optimize the treatment plan, from the initial single drug treatment to the combined treatment plan, and the new adjuvant treatment before cancer surgery, continuously promote the treatment process of pancreatic cancer, and improve the quality of life of patients with pancreatic cancer (52). With the development of tumor molecular biology, more and more therapeutic targets will be discovered and recognized. Improving the effective rate without increasing toxicity is the development direction of targeted therapy. It is believed that in the future, GEM synthetic preparations with low toxicity, good therapeutic effect, and long half-life will be developed to play a better role in the first line of anti-cancer.

This study had several shortcomings. Firstly, some of the selected studies were non-blind trials, and the research quality was slightly deficient. Secondly, most of the studies included only Asian patients were (mostly in China and Japan) in the GEM plus S-1 group, and there was no research comparison on ethnic differences. Therefore, the results may only be applicable to Asian patients; whether the research results are applicable to patients in other regions needs more research to confirm. Finally, the included literature did not provide detailed data on the quality-of-life scale and cost-effectiveness, so the project could not be analyzed. It can be speculated that the treatment cost of the combined chemotherapy group will certainly increase due to the increased use of chemotherapeutic drugs and the subsequent occurrence of more side effects.

Conclusions

This meta-analysis showed that OS, PFS, 1-year survival rate, and ORR of GEM-based combination therapy were statistically significantly improved, although the AEs were also increased. Subgroup analysis showed that the efficacy of GEM plus CAP and GEM plus S-1 was better than that of GEM alone, while GEM plus CIS did not show superiority. The existing evidence suggested that the combination therapy had better efficacy and higher survival benefit than GEM alone. However, considering the high rate of AEs

and latent economic problems, clinicians need to consider the patient's condition, treatment willingness, and financial situation. In addition, how to further reduce AEs is worthy of further study.

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Footnote

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