JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(5)432–441
doi:10.1093/jjco/hyp198
Advance Access Publication 10 February 2010

Gemcitabine-based Cytotoxic Doublets Chemotherapy for Advanced Pancreatic Cancer: Updated Subgroup Meta-analyses of Overall Survival

De-rong Xie†, Qiong Yang†, Deng-lin Chen, Zhi-min Jiang, Zhuo-fei Bi, Wen Ma and Yuan-dong Zhang

Department of Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

For reprints and all correspondence: De-rong Xie, Department of Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China. E-mail: xiederong@21cn.com
†D.-r. Xie and Q. Yang are equal contributors and co-first authors to this paper.

Received November 12, 2009; accepted December 20, 2009

Objective: Previous meta-analyses showed a survival advantage with gemcitabine (GEM)-based combinations over GEM in advanced pancreatic cancer. Therefore, it would be valuable to explore the specific active regimens based on a subgroup meta-analysis.
Methods: Updated data by comprehensive search of the literature from databases and conference proceedings. Subgroup meta-analysis compared GEM with GEM-based doublets chemotherapy in terms of 6-month overall survival (OS) and 1-year OS.
Results: Eighteen randomized controlled trials with 4237 patients were included, which were divided into five subgroups: GEM/capecitabine, GEM/cisplatin, GEM/5-fluorouracil, GEM/irinotecan and GEM/oxaliplatin. In each subgroup, risk ratios (RRs) for 6-month OS were 0.85 ($P = 0.04$), 0.99 ($P = 0.88$), 0.95 ($P = 0.46$), 1.03 ($P = 0.77$) and 0.80 ($P = 0.001$), respectively, and RRs for 1-year OS were 0.94 ($P = 0.14$), 0.99 ($P = 0.75$), 0.96 ($P = 0.19$), 1.00 ($P = 0.97$) and 0.93 ($P = 0.05$), respectively. A meta-analysis of the trials with adequate information on performance status (PS) was performed in four trials with 1325 patients. Patients with a good PS did not show a survival benefit when receiving combination chemotherapy. RRs for 6-month and 1-year OS were 0.82 ($P = 0.18$) and 0.93 ($P = 0.08$). In contrast, application of combination chemotherapy to patients with a poor PS appeared to be harmful. RRs were 1.17 ($P = 0.04$) for 6-month OS and 1.09 ($P = 0.04$) for 1-year OS.
Conclusions: The meta-analysis indicated a significant survival benefit when GEM was either combined with capcitabine or oxaliplatin. On the basis of a preliminary subgroup analysis, pancreatic cancer patients with a poor PS appeared to have a worse survival benefit from GEM-based cytotoxic doublets.

Key words: pancreatic neoplasms – gemcitabine – capecitabine – oxaliplatin – meta-analysis

INTRODUCTION

Pancreatic cancer is a fetal disease. The majority (80%) of pancreatic cancer are metastatic at the time of diagnosis (1). Gemcitabine (GEM) is currently considered as a standard treatment for patients with advanced pancreatic cancer (APC). However, patients treated with GEM alone still have a poor prognosis; the result was disappointing with a clinical benefit response of 23.8%, median overall survival (mOS) of 5.65 months and 1-year OS rate of 18% (2).

In an effort to improve therapeutic efficacy, numerous randomized trials have investigated GEM-based combination regimens adding a second cytotoxic agent such as cisplatin, oxaliplatin, 5-fluorouracil, capecitabine, irinotecan, exatecan or pemetrexed. Though the data showed significant improvement in OS by the addition of capecitabine to GEM over GEM alone in APC in the interim analysis of trial conducted by Cunningham et al. (3), the final data indicated no substantial OS advantage (4).

In 2006, we published a meta-analysis which showed that GEM-based combination chemotherapy has a substantial OS advantage compared with GEM alone in patients with APC (5). More recently, three other meta-analyses confirmed

our conclusion (6–8). However, these data just suggested that APC patients might benefit from GEM-based combination chemotherapy, even though the study of Heinemann indicated a significant survival benefit when GEM was either combined with platinum analogues or fluoropyrimidines (6). In contrast, one meta-analysis published in 2007 suggested that GEM/platinum combinations appeared to improve progress free survival (PFS) and objective response rate (ORR) in selected patients without OS benefit (9). In summary, there was little high-level evidence to support a specific cytotoxic agent combined with GEM that should be used for the treatment of patients with APC in clinical practice.

To explore exactly active regimens, we updated the data and carried out a subgroup meta-analysis. The present meta-analysis mainly evaluates these regimens, which were frequently used in clinical trials. The primary end point was 6-month OS after randomization, and the secondary end point was 1-year OS. These trials were grouped into five separate subgroups according to the second cytotoxic agent added to GEM, which were GEM plus capecitabine (GEMCAP), GEM plus cisplatin (GEMDDP), GEM plus 5-fluorouracil (GEMFU), GEM plus irinotecan (GEMIRI) and GEM plus oxaliplatin (GEMOX).

METHODS

Literature Search

Updated results of the eligible randomized controlled trials (RCTs) were gathered through Medline, EMBASE, CBMdisc, ASCO abstracts, and with the addition of ESMO abstracts (2008) and ECCO abstracts (2007) after the last search on 26 April 2006 (5). Keywords used in the search were as follows: pancreas, pancreatic cancer, pancreatic neoplasms, pancreatic carcinoma, pancreatic adenocarcinoma, gemzar and GEM. No language restrictions were applied. The deadline of this search was on 31 May 2009. At last, 516 potentially eligible abstracts were collected.

Selection Criteria

Study Design

The trials should be prospective, properly randomized, and matched for ages, stages and performance status (PS).

Study Population

Patients eligible for the study were those with histological or cytological diagnosis of pancreatic cancer that was locally advanced or metastatic and not amenable to curative surgical resection. Furthermore, a baseline Karnofsky performance status (KPS) of $\geq$50% and adequate haematological, renal, cardiac and hepatic functions were required. Patients with estimated life expectancy of at least 12 weeks should have no prior chemotherapy, no prior radiation therapy and other anti-tumour therapy in the previous 6 months prior to the study entry.

Interventions

The treatment group received GEM-based cytotoxic doublets chemotherapy. The control group received GEM alone.

Types of Outcomes

The primary outcome measurement was OS, which should have a clear data of survival or survival curve. The follow-up rate should be above 95%.

Data Collection and Analysis

Two primary reviewers assessed all the abstracts that were identified from the sources mentioned above. Both reviewers independently selected the trials according to prior agreement regarding the study population and the interventions. If one of the reviewers concluded that an abstract might be eligible, the complete article was retrieved and reviewed in detail by two reviewers. Then the trial would be included in the meta-analysis according to the selection criteria and the follow-up information was obtained from each trial: year of publication, number of patients, PS, chemotherapy regimen and OS. Missing data from the primary study reports were requested from the investigators. If the same trials were found in different publications, then the final data of the trial were chosen for analysis. Methodological quality of the trials was assessed using a validated scale (range, 0–5) and was applied to items that influence intervention efficacy. The scale consisted of items pertaining to randomization, masking, dropouts and withdrawals, which was reported by Jadad et al. (10).

Statistical Analysis

The primary end point was 6-month OS after randomization. The secondary end point was 1-year OS. All variables were defined as dichotomous data. We standardized the resulting treatment effect to obtain an effect size by risk ratio (RR). RR is defined as a ratio of the risk of death in the GEM-based doublets group divided by the risk of death in the GEM alone group. Crude RRs with 95% confidence intervals (CIs) were used to assess the risk of death between the GEM-based doublets group and the GEM alone group. The significance of the pooled RR was determined by the Z-test, and $P < 0.05$ was considered as statistically significant (11). To evaluate the regimen-specific and PS-specific effect, subgroup analysis was conducted on the basis of different regimens and performance statuses.

Heterogeneity assumption was checked by a χ^2-based Q-test (12). A P value of more than 0.10 for the Q-test indicated a lack of heterogeneity across the studies, so the

pooled estimation of the RRs of each study was calculated by the fixed effects model (Mantel–Haenszel method). Otherwise, the random effects model (DerSimonian and Laird method) was used. One-way sensitivity analysis was performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled RR (11). An estimate of the potential publication bias was carried out by the funnel plot, in which the standard error (SE) of log(RR) of each study was plotted against its log(RR). An asymmetric plot suggested a possible publication bias. The funnel plot asymmetry was assessed by Egger's test—a linear regression approach to measure the funnel plot asymmetry on the natural logarithmic scale of the RR. The significance of the intercept was determined by the t-test suggested by Egger; $P < 0.05$ was considered a representative of statistically significant publication bias (13). All the statistical tests for our meta-analysis were performed with STATA version 10.0 (Stata Corporation, College Station, TX, USA). Two-sided P values were used.

RESULTS

Trial Flow

The flow chart of selection of RCTs for meta-analysis was shown in Fig. 1. After updating, 18 RCTs involving 4237 patients were included in the present meta-analysis at last (3,14–30). All the RCTs were grouped according to the combination chemotherapy regimen, and subgroup meta-analysis was performed after grouping. There were 935 patients from three RCTs in the GEMCAP group (3,14,15), 958 randomized patients from seven RCTs in the GEMDDP group (16–22), 881 patients from three RCTs in the GEMFU group (23–25), 579 patients from three RCTs in the GEMIRI group (18,26,27) and 929 patients from three RCTs in the GEMOX group (28–30).

Characteristics of Selected Trials

These prospective randomized controlled studies were summarized in Table 1. All selected trials were included strictly according to the prior selection criteria, which were

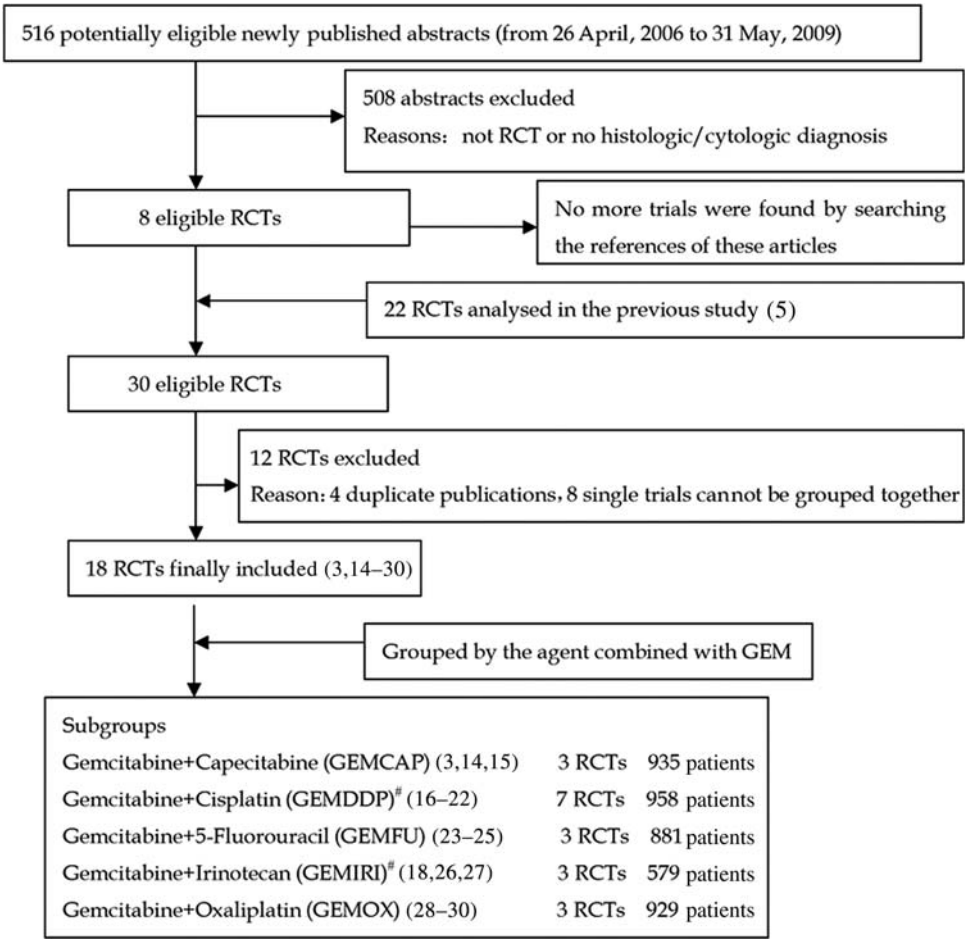

Figure 1. Flow chart of selection of RCTs for meta-analysis. #Trial of (18) included four randomization groups, which were GEM, GEM + Docetaxel, GEM + Cisplatin and GEM + Irinotecan. Therefore, it was included in the GEMDDP and the GEMIRI subgroup meta-analysis for two times. RCT, randomized controlled trial; GEM, gemcitabine.

Table 1. Characteristics of eligible randomized controlled trials

Trials	Interventions	Patients	6-Month OS (%)	1-Year OS (%)	Jadad score
Scheithauer (14)	Gem	42	59.4	37.2	3
	Gem + Capecitabine	41	67.7	31.8	
Cunningham (3)	Gem	266	50.0	18.8	3
	Gem + Capecitabine	267	61.8	26.2	
Herrmann (15)	Gem	159	61.0	30.0	3
	Gem + Capecitabine	160	59.0	32.0	
Colucci (16)	Gem	54	31.5	11.0	3
	Gem + Cisplatin	53	47.0	11.3	
Wang (17)	Gem	20	81.3	31.3	3
	Gem + Cisplatin	22	61.6	11.1	
Kulke (18)	Gem	45	53.3	NA	3
	Gem + Cisplatin	45	51.1	NA	
	Gem + Docetaxel	49	44.9	NA	
	Gem+ Irinotecan	44	44.7	NA	
Li (19)	Gem	25	20.3	13.6	3
	Gem + Cisplatin	21	31.1	6.3	
Viret (20)	Gem	41	58.3	25.1	3
	Gem + Cisplatin	42	55.5	32.4	
Heinemann (21)	Gem	97	48.6	22.5	3
	Gem + Cisplatin	95	59.4	27.5	
Colucci (22)	Gem	199	61.0	34.0	3
	Gem + Cisplatin	201	56.0	30.7	
Di Costanzo (23)	Gem	49	59.0	14.5	3
	Gem + 5-FU	44	59.0	23.3	
Berlin (24)	Gem	162	42.0	15.5	3
	Gem + 5-FU	160	55.0	21.9	
Riess (25)	Gem	236	53.0	20.0	3
	Gem + 5-FU/CF	230	49.0	20.0	
Rocha Lima (26)	Gem	180	52.9	22.0	3
	Gem + Irinotecan	180	50.7	21.0	
Stathopoulos (27)	Gem	70	50.0	21.8	3
	Gem + Irinotecan	60	60.0	24.3	
Louvet (28)	Gem	156	60.4	27.8	3
	Gem + Oxaliplatin	157	68.0	34.7	
Poplin (29)	Gem	280	42.1	17.1	3
	Gem + Oxaliplatin	276	52.2	21.0	
Yan (30)	Gem	30	20.0	10.0	2
	Gem + Oxaliplatin	30	53.3	16.7	

OS, overall survival; NA, not available.

prospective, randomized, and balanced for age, sex, stage and PS. Patients eligible for these studies had histologically or cytologically ascertained pancreatic cancer and the same baseline data, which showed no evidence of selection bias in the course of trials recruitment. However, between the different trials a considerable degree of variation can be detected. For example, GEM was given as either standard 30-min infusion or as fixed dose rate infusion with 10 mg/m^2/min in different trials. Of the 18 trials, four trials were randomized Phase II trials and the others were randomized

Phase III trials. Most of the selected studies were considered to be of high quality as reflected by their achieving a score of three points or higher in Jadad's scale except for the trial conducted by Yan (30). The data of 6-month OS and 1-year OS were extracted from each of these 18 trials.

Overall Survival

Meta-analysis of 18 RCTs

Four thousand, two hundred and thirty-seven randomized patients from 18 RCTs, 2128 in the GEM combination group and 2109 in the GEM alone group, were included in the meta-analysis of 6-month OS. The result of the test for heterogeneity of the treatment effect was not significant ($P > 0.10$). Therefore, a fixed effects model was selected in meta-analysis. Compared with GEM monotherapy, GEM-based cytotoxic doublets chemotherapy reduced the risk of death by 9% in 6-month OS (RR = 0.91, 95% CI: 0.85 – 0.97, $P = 0.005$). With the same technique, 4103 patients from 17 RCTs were included in the meta-analysis of 1-year OS. Compared with GEM monotherapy, GEM-based cytotoxic doublets chemotherapy reduced the risk of death by 4% in 1-year OS (RR = 0.96, 95% CI: 0.93 – 0.99, $P = 0.02$). More details are shown in Table 2.

Subgroup Meta-analysis of Different Regimens

Five separate subgroups (GEMCAP, GEMDDP, GEMFU, GEMIRI and GEMOX) were evaluated. For 6-month OS, GEMCAP and GEMOX reduced the risk of death by 15% (RR = 0.85, 95% CI: 0.73 – 0.99, $P = 0.04$) and 20% (RR = 0.80, 95% CI: 0.70 – 0.91, $P = 0.001$), respectively. The other three regimens did not significantly improve OS. For 1-year OS, the subgroup meta-analysis had shown that GEMOX potentially reduced the risk of death by 7% (RR = 0.93, 95% CI: 0.87 – 1.00, $P = 0.05$), the other four regimens did not show a survival benefit. More details about 6-month OS and 1-year OS are presented in Figs 2 and 3 and Table 2.

Subgroup Meta-analysis of PS

Subgroup analysis divided patients into a good PS group (KPS = 90–100, ECOG 0–1) or a poor PS group (KPS = 60–80, ECOG 2). Four trials provided the survival data on two different performance statuses (14,24,25,27). In the good PS group, GEM-based doublets did not show survival advantage over GEM alone; the RRs for 6-month and 1-year OS were 0.82 (95% CI: 0.62 – 1.09, $P = 0.18$) and 0.93 (95% CI: 0.85 – 1.01, $P = 0.08$), respectively. In the poor PS group, the RRs were 1.17 (95% CI: 1.01 – 1.36, $P = 0.04$) for 6-month OS and 1.09 (95% CI: 1.01 – 1.19, $P = 0.04$) for 1-year OS, respectively. GEM-based cytotoxic doublets chemotherapy increased the risk of death in patients with poor PS in APC.

Sensitivity Analysis

Sensitivity analysis was performed by sequential omission of individual studies from various contrasts. For the meta-analysis of 18 RCTs, when the trial conducted by Cunningham which was the only one of selected randomized trials that showed GEM-based cytotoxic doublets chemotherapy significantly improved OS over GEM alone (3) was omitted, the pooled RR and 95% CIs for 1-year OS was changed, but the pooled RR and 95% CIs for 6-month OS was not changed. This indicated that GEM-based doublets improved the OS of APC patients indeed, especially for 6-month OS.

Publication Bias Assessment

Begg's funnel plot and Egger's test were performed to access the publication bias of literatures. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (Fig. 4). Then, Egger's test was used to provide statistical evidence of the funnel plot symmetry. The results still did not suggest any evidence of publication bias ($P = 0.63$ for

Table 2. Main results of pooled risk ratio for overall survival (GEM-based doublets vs. GEM alone)

Subgroups	6-Month OS			1-Year OS		
	RR (95% CI)	P*	$P_h^\dagger$	RR (95% CI)	P*	$P_h^\dagger$
GEMCAP	0.85 (0.73, 0.99)	0.04	0.15	0.94 (0.87, 1.02)	0.14	0.41
GEMDDP	0.99 (0.86, 1.13)	0.88	0.27	0.99 (0.91, 1.07)	0.75	0.05
GEMFU	0.95 (0.83, 1.09)	0.46	0.08	0.96 (0.90, 1.02)	0.19	0.36
GEMIRI	1.03 (0.86, 1.22)	0.77	0.56	1.00 (0.91, 1.10)	0.97	0.59
GEMOX	0.80 (0.70, 0.91)	0.001	0.32	0.93 (0.87, 1.00)	0.05	0.77
Total	0.91 (0.85, 0.97)	0.005	0.07	0.96 (0.93, 0.99)	0.02	0.31

GEM, gemcitabine; OS, overall survival; RR, risk ratio; CI, confidence interval; GEMCAP, gemcitabine plus capecitabine; GEMDDP, gemcitabine plus cisplatin; GEMFU, gemcitabine plus 5-fluorouracil; GEMIRI, gemcitabine plus irinotecan; GEMOX, gemcitabine plus irinotecan.
*P value of significance tests of RR = 1; $^\dagger P_h$ value of heterogeneity tests.

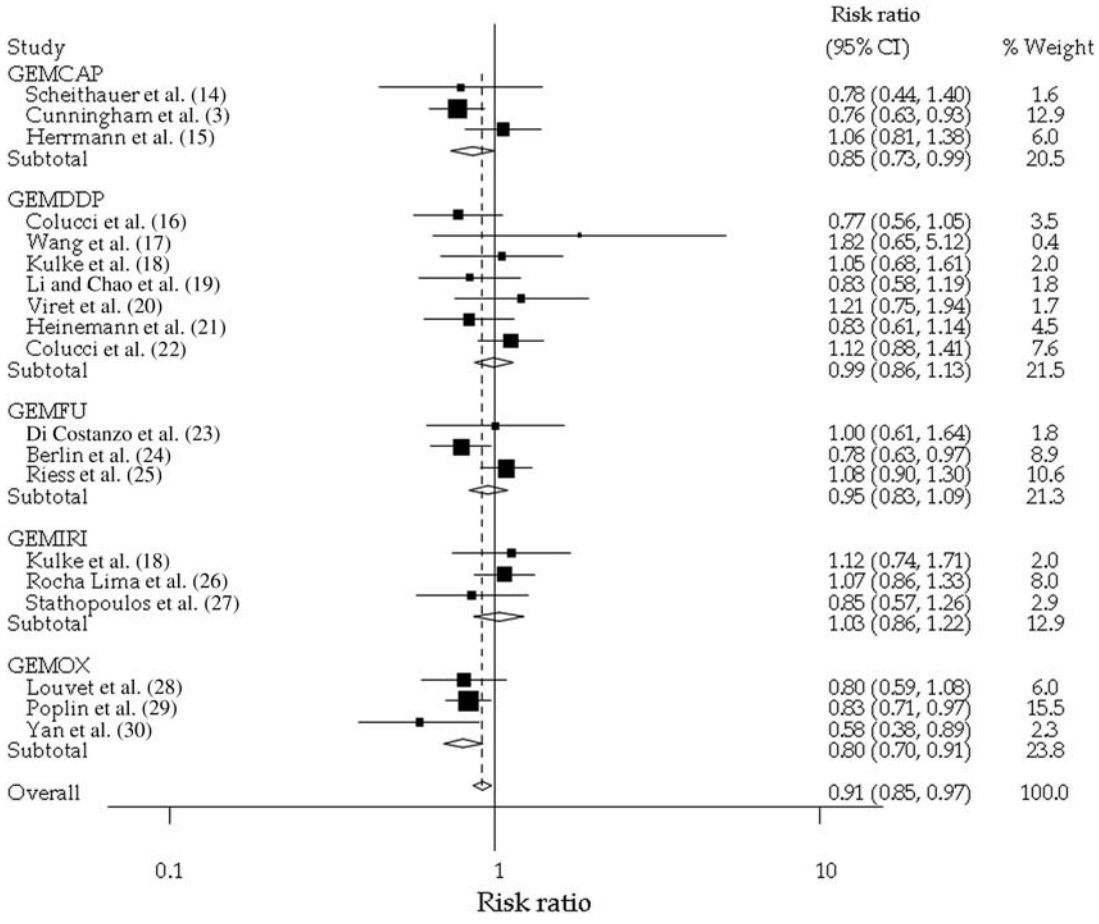

Figure 2. Forest plot of subgroup meta-analysis for 6-month OS. The diamonds stood for pooled effect. If the diamonds were located on the left of the vertical line, then pooled effect favoured gemcitabine-based doublets. OS, overall survival.

6-month OS total analysis, $P = 0.64$ for 1-year OS total analysis, respectively).

DISCUSSION

The present study showed a significant additional survival advantage of GEM-based cytotoxic doublets chemotherapy compared with GEM alone through meta-analysis of 4237 patients from 18 RCTs. GEM-based cytotoxic doublets chemotherapy resulted in 9% reduction of the risk of death in 6-month OS (RR = 0.91, 95% CI: 0.85 – 0.97, $P = 0.005$) and 4% reduction of the risk of death in 1-year OS (RR = 0.96, 95% CI: 0.93 – 0.99, $P = 0.02$). Our previous study and three other studies showed a similar result (5–8). However, our result might be more practical for a clinician because we reduced interference effect of targeted drugs on the result of our meta-analysis by only including the trials comparing GEM plus cytotoxic agents with GEM.

Sharing the similar anti-tumour mechanism—inhibiting thymidylate synthase—capecitabine is usually considered as an alternative for 5-fluorouracil; however, this might not be true in some cases. So, we divided them into two different subgroups in this meta-analysis, which was different from research design in the study of Heinemann (6). The present meta-analysis showed that GEMCAP was superior to GEM in 6-month OS (RR = 0.85, 95% CI: 0.73 – 0.99, $P = 0.04$), but did not improve 1-year OS (RR = 0.94, 95% CI: 0.87 – 1.02, $P = 0.14$). To explore the impact of negative final result reported by Cunningham et al. (4) on the conclusion of our meta-analysis, we used the final data and did a meta-analysis again. The results for the meta-analysis of 18RCTs and subgroup meta-analysis of different regimens were not yet changed (data not shown). For GEMCAP vs. GEM alone, pooled RRs for 6-month/1-year OS were 0.86 (95% CI: 0.74 – 1.00, $P = 0.04$) and 0.97 (95% CI: 0.90 – 1.05, $P = 0.47$), respectively. In contrast, GEMFU did not show a survival benefit in 6-month OS (RR = 0.95, 95% CI: 0.83 – 1.09, $P = 0.46$) and 1-year OS (RR = 0.96, 95% CI: 0.90 – 1.02, $P = 0.19$). When we combined these data and performed the meta-analysis, we also found that GEM plus CAP/5-FU improved the 6-month OS and 1-year OS (data not shown). In summary, we concluded that GEMCAP, but not GEMFU, may be an option of first-line palliative chemotherapy for APC, which is different from the conclusion reported by Heinemann (6).

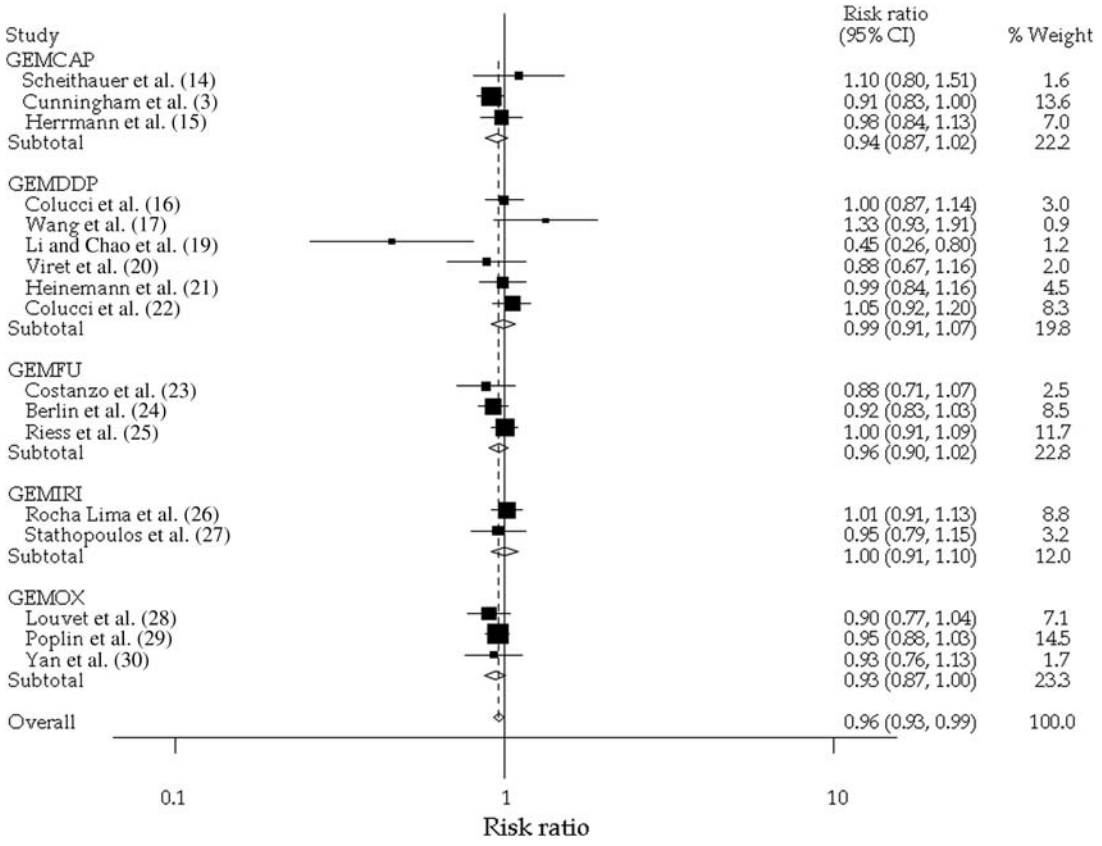

Figure 3. Forest plot of subgroup meta-analysis for 1-year OS. The diamonds stood for pooled effect. If the diamonds were located on the left of the vertical line, then pooled effect favoured gemcitabine-based doublets.

GEMDDP did not improve the 6-month OS (RR = 0.99, 95% CI: 0.86 – 1.13, $P = 0.88$) and 1-year OS (RR = 0.99, 95% CI: 0.91 – 1.07, $P = 0.75$) in APC. Similarly, the study reported by Boeck et al. showed that GEMDDP regimen could not improve the OS, but subgroup analysis indicated that KPS score was an important prognosis factor (31). To the patients of KPS 90 – 100, the combination chemotherapy group gained longer median survival time as compared with the control group (322 vs. 206 days, $P = 0.051$). On the other hand, to the patients of KPS 70 – 80, two groups had similar median survival time (143 vs. 147 days, $P = 0.64$). In our present meta-analysis, poor PS played a negative role on GEM-based cytotoxic doublets chemotherapy in patients with APC. In summary, patients in poor PS will not benefit from GEMDDP, but patients in good PS have a potential benefit. The NCCN (2009 v1) guidelines suggested that GEMDDP regimen might apply to patients with good PS.

Controversy over GEMOX regimen was quite vehement. Louvet et al. (28) reported that GEMOX significantly improved the response rate and clinical benefit response. According to the result, NCCN guideline (2006) recommended GEMOX as front-line chemotherapy in patients with APC. However, the study of Poplin et al. (29) suggested a negative result, though a trend of improvement in median survival time was showed (6.5 month for GEMOX vs. 5 month for GEM), which was awarded as one of the major clinical cancer advances in 2006 by ASCO (32). There was a good homogeneity between two RCTs because treatment plans and dose adaptations were the same in the treatment or control group of two RCTs. Another study reported by Yan et al. (30) used biweekly GEMOX to treat APC, and showed better tumour control rate and 6-month/1-year OS. In our meta-analysis, there was no heterogeneity among three studies ($P = 0.32$, data not shown) and there was an advantage of 6-month OS (RR = 0.80, 95% CI: 0.70 – 0.91, $P = 0.001$) for the GEMOX group with a trend of improvement in 1-year OS (RR = 0.93, 95% CI: 0.87 – 1.00, $P = 0.05$). Evidences available indicated a good prospect of the clinical use of GEMOX, which deserved further clinical research.

GEM plus irinotecan was not usually used in pancreatic cancer and meta-analysis of three RCTs did not show survival benefit in patients with APC. Therefore, there was no evidence supporting the use of combination chemotherapy of GEM combined with irinitecan in patients with APC.

PS might be an important prognostic factor for OS in APC. Meta-analysis of four trials did not indicate that GEM-based cytotoxic doublets chemotherapy has a survival benefit. For patients with poor PS, in contrast, GEM-based cytotoxic doublets chemotherapy increased the risk of death in patients with poor PS in APC. The RRs were 1.17 (95% CI: 1.01 – 1.36, $P = 0.04$) for 6-month OS and 1.09 (95% CI: 1.01 – 1.19, $P = 0.04$) for 1-year OS, respectively.

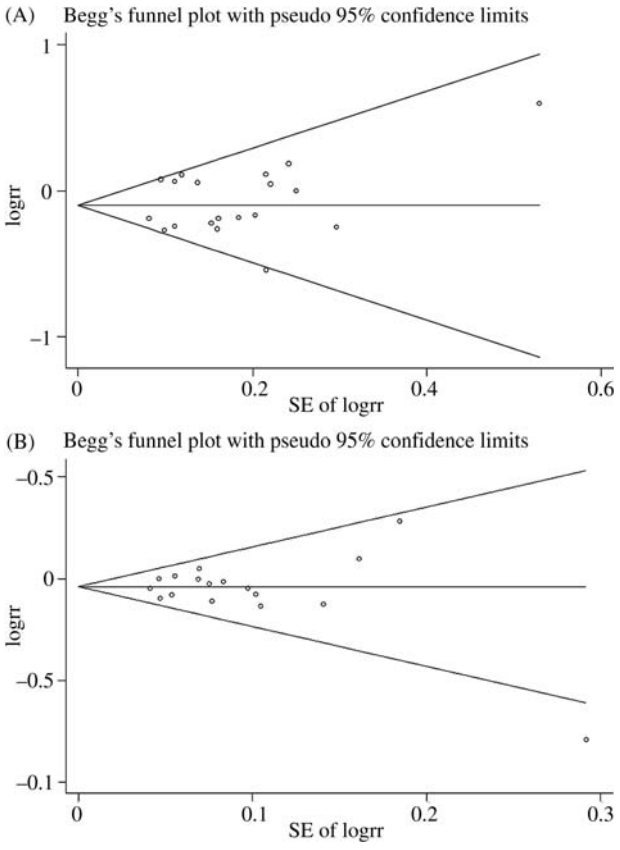

Figure 4. Begg's funnel plot of test for publication bias. (A) Publication bias in analysing 6-month OS. (B) Publication bias in analysing 1-year OS. The horizontal line represents the meta-analysis summary estimate and the diagonal lines represent the pseudo-95% CI limits about the effect estimate. In the absence of publication bias, studies will be distributed symmetrically above and below the horizontal line. Asymmetry on the top of the graph indicates the evidence of publication bias towards studies reporting a positive logrr (increased risk of death in GEM-based doublets chemotherapy group). logrr, natural logarithm of the RR; SE of logrr, standard error of the logrr.

Meta-analysis of Heinemann (6) indicated that pancreatic cancer patients with a good PS appear to benefit from GEM-based cytotoxic combinations, whereas patients with a poor PS seem to have no survival benefit from combination chemotherapy. To interpret the differences in two meta-analyses and study results more reasonably, one issue that should be kept in mind was that only four or five trials with adequate survival data on different PS were included and analysed. Therefore, a prospective evaluation of this issue is strongly recommended for future clinical trials in APC.

To date, four other meta-analyses evaluating chemotherapy in APC have been published (6–9). Three of them showed that GEM-based combination chemotherapy may be superior to single-agent GEM regarding OS (6–8), and another meta-analysis only indicated that platinum/GEM combinations appeared to improve PFS and ORR (9). The most promising survival advantage was observed when GEM was combined with either a platinum compound or fluoropyrimidines in the above-mentioned meta-analyses. In contrast, our data supported that APC patients might get OS benefit from the specific active regimens (GEM plus capecitabine or GEM plus oxaliplatin). In addition, our meta-analysis differs from these analyses in methodological and clinical aspects. First, 6-month OS was chosen as a primary end point to explore the difference between GEM-based cytotoxic doublets and GEM alone. Second, our data were more comprehensive and updated, in which one trial reported in 2009 ASCO annual meeting was included (22). At last, our meta-analysis included only Phase II/III clinical trials which compared GEM plus a second cytotoxic agent (target drugs were excluded) with GEM alone in APC.

This subgroup meta-analysis was based on RCTs with high quality. We carried out a comprehensive search of the literature from barely all of cancer database. Publication bias is frequently cited as a reason for the lack of validity in meta-analysis. Publication bias could occur if studies that found no association between exposure and disease were less likely to be submitted and accepted for publication than studies that found a positive association. In fact, the results of the majority of the studies included in our meta-analyses were negative, as stated by the authors. Begg's funnel plot and Egger's test showed less evidence of publication bias. Therefore, this subgroup meta-analysis provided a valid assessment and creditable results.

Several technical issues have to be mentioned regarding this meta-analysis. One major limitation is that some data source was extracted from abstracted data and not individual patient data (IPD). In general, an IPD-based meta-analysis would give a more robust estimation for the association. Therefore, our results need to be interpreted with care, especially for the subgroup meta-analysis of PS. Few survival data about different PS limited the validity of present meta-analysis of PS. In addition, the hazard ratio (HR) for OS would be appropriate to evaluate survival benefit in the meta-analysis. However, RR was chosen as surrogate end point for OS because of less adequate information on HR in several selected trials. Publication bias is a significant threat to the validity of meta-analysis. Although we detected no evidence of publication bias using the graphical method, it is difficult to completely rule out this possibility. Heterogeneity among trials can be another limitation of our meta-analysis; there were still many factors causing heterogeneity, such as different dose of drug, two infusion methods of GEM and so on. In the present meta-analysis, the result of the test for heterogeneity of the treatment effect was not significant ($P > 0.10$).

In conclusion, our data showed that GEM-based combination chemotherapy had a substantial OS advantage compared with GEM alone in patients with APC, especially when GEM was either combined with capcitabine or oxaliplatin. On the basis of a preliminary subgroup analysis, pancreatic cancer patients with a poor PS appeared to have a worse survival benefit from GEM-based cytotoxic doublets chemotherapy. However, significant advantage of

combination chemotherapy over GEM alone only be revealed when the sample was large enough. For example, 4237 patients were included in the present meta-analysis. This suggested that GEM-based cytotoxic doublets chemotherapy achieved efficacy stage in the treatment of APC at present. Though we think that GEM-based cytotoxic doublets chemotherapy should be considered as first-line treatment for APC at present, to improve the efficacy, new agents should be tested and separate treatment strategies for patients with good and poor PS should be considered in future prospective clinical trials.

Acknowledgements

We thank Professor C. Louvet, C.M. Rocha Lima and R. Herrmann for their kind help in providing detailed survival data. We also thank Dr B. Chen and Y.Y. Huang for their assistance in the use of Stata software.

Funding

This work was supported by a grant from the Science and Technology Program Foundation of Guangdong Province, China (No. 2009B030801195).

Conflict of interest statement

None declared.

References

1. Yeo CJ, Yeo TP, Hruban RH, Kern SE, Iacobuzio-Donohue CA, Maitra A, et al. Cancer of the pancreas. In: Devita VT, Jr, Hellman S, Rosenberg SA, editors. *Cancer: Principles & Practice of Oncology*, 5th edn. Philadelphia, USA: Lippincott Williams & Wilkins, 2005;945.
2. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with GEM as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403–13.
3. Cunningham D, Chau I, Stocken D, Davies C, Dunn J, Valle J, et al. Phase III randomised comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. European Cancer Conference (ECCO 13). *Eur J Cancer* 2005;3(Suppl):12 (Abstract PS11).
4. Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009;27:5513–8.
5. Xie DR, Liang HL, Wang Y, Guo SS, Yang Q. Meta-analysis on inoperable pancreatic cancer: a comparison between gemcitabine-based combination therapy and gemcitabine alone. *World J Gastroenterol* 2006;12:6973–81.
6. Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer* 2008;8:82.
7. Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol* 2007;25:2607–15.
8. Banu E, Banu A, Fodor A, Landi B, Rougier P, Chatellier G, et al. Meta-analysis of randomised trials comparing gemcitabine-based doublets versus gemcitabine alone in patients with advanced and metastatic pancreatic cancer. *Drugs Aging* 2007;24:865–79.
9. Bria E, Milella M, Gelibter A, Cuppone F, Pino MS, Ruggeri EM, et al. Gemcitabine-based combinations for inoperable pancreatic cancer: have we made real progress? A meta-analysis of 20 phase 3 trials. *Cancer* 2007;110:525–33.
10. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of report of randomized clinical trials: is blinding necessary? *Controlled Clin Trials* 1996;17:1–12.
11. Aurelio T. Assessing the influence of a single study in the meta-anyalysis estimate. *Stata Tech Bull* 1999;8:15–17.
12. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997;127:820–6.
13. Egger M, Davey Smith G, Schneider M, Minder C. Bias in metaanalysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
14. Scheithauer W, Schüll B, Ulrich-Pur H, Schmid K, Raderer M, Haider K, et al. Biweekly high-dose gemcitabine alone or in combination with capecitabine in patients with metastatic pancreatic adenocarcinoma: a randomized phase II trial. *Ann Oncol* 2003;14:97–104.
15. Herrmann R, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schüller J, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for clinical cancer research and the Central European Cooperative Oncology Group. *J Clin Oncol* 2007;25:2212–7.
16. Colucci G, Giuliani F, Gebbia V, Biglietto M, Rabitti P, Uomo G, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. *Cancer* 2002;94:902–10.
17. Wang XY, Ni QX, Jin ML, Li Z, Wu Y, Zhao Y, et al. Gemcitabine or gemcitabine plus cisplatin for in 42 patients with locally advanced or metastatic pancreatic cancer. *Chin J Oncol* 2002;24:404–7 (in Chinese).
18. Kulke MH, Niedzwiecki D, Tempero MA, Hollis DR, Mayer RJ. A randomized phase II study of gemcitabine/cisplatin, gemcitabine fixed dose rate infusion, gemcitabine/docetaxel, or gemcitabine/irinotecan in patients with metastatic pancreatic cancer (CALGB 89904). *J Clin Oncol* 2004;22:4011.
19. Li CP, Chao Y. A prospective randomized trial of gemcitabine alone or gemcitabine + cisplatin in the treatment of metastatic pancreatic cancer. *J Clin Oncol* 2004;22:140.
20. Viret F, Ychou M, Lepille D, Mineur L, Navarro F, Topart D, et al. Gemcitabine in combination with cisplatin (GP) versus gemcitabine (G) alone in the treatment of locally advanced or metastatic pancreatic cancer: final results of a multicenter randomized phase II study. *J Clin Oncol* 2004;22:4118.
21. Heinemann V, Quietzsch D, Gieseler F, Gonnermann M, Schönekäs H, Rost A, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 2006;24:3946–52.
22. Colucci G, Labianca R, Di Costanzo F, Gebbia V, Cartenì G, Massidda B, et al. A randomized trial of gemcitabine (G) versus G plus cisplatin in chemotherapy-naive advanced pancreatic adenocarcinoma: the GIP-1 (Gruppo Italiano Pancreas—GOIM/GISCAD/GOIRC) study. *J Clin Oncol* 2009;27:4504.
23. Di Costanzo F, Carlini P, Doni L, Massidda B, Mattioli R, Iop A, et al. Gemcitabine with or without continuous infusion 5-FU in advanced pancreatic cancer: a randomised phase II trial of the Italian oncology group for clinical research (GOIRC). *Br J Cancer* 2005;93:185–9.
24. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB 3rd. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol* 2002;20:3270–5.
25. Riess H, Helm A, Niedergethmann M, Schmidt-Wolf I, Moik M, Hammer C, et al. A randomised, prospective, multicenter, phase III trial of gemcitabine, 5-fluorouracil (5-FU), folinic acid vs. gemcitabine alone in patients with advanced pancreatic cancer. *J Clin Oncol* 2005;23:4009.

26. Rocha Lima CM, Green MR, Rotche R, Miller WH, Jr, Jeffrey GM, Cisar LA, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* 2004;22:3776–83.
27. Stathopoulos GP, Syrigos K, Aravantinos G, Polyzos A, Papakotoulas P, Fountzilas G, et al. A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *Br J Cancer* 2006;95:587–92.
28. Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, André T, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005;23:3509–16.
29. Poplin E, Levy DE, Berlin J, Rothenberg M, Cella D, Mitchell E, et al. Phase III trial of gemcitabine (30-minute infusion) versus gemcitabine (fixed-dose-rate infusion [FDR]) versus gemcitabine + oxaliplatin (GEMOX) in patients with advanced pancreatic cancer (E6201). *J Clin Oncol* 2006;24:LBA4004.
30. Yan ZC, Hong J, Xie G. Observation of therapeutic efficacy of a biweekly regimen of Gemzar plus oxaliplatin for 30 cases with advanced pancreatic cancer. *Chin J Clin Oncol* 2007;34:322–5 (in Chinese).
31. Boeck S, Hinke A, Wilkowski R, Heinemann V. Analysis of prognostic factors in patients with advanced pancreatic cancer: subgroup analysis of a randomized phase III trial comparing single-agent gemcitabine to the gemcitabine plus cisplatin combination. *J Clin Oncol* 2005;23:4105.
32. Ozols RF, Herbst RS, Colson YL, Gralow J, Bonner J, Curran WJ Jr, et al. Clinical cancer advances 2006: major research advances in cancer treatment, prevention, and screening—a report from the American Society of Clinical Oncology. *J Clin Oncol* 2007;25:146–62.