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CLINICAL RESEARCH

Meta-analysis on inoperable pancreatic cancer: A comparison between gemcitabine-based combination therapy and gemcitabine alone

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Abstract

AIM: To compare gemcitabine-based combination therapy and gemcitabine (GEM) alone in patients with advanced pancreatic cancer (APCa) through meta-analysis.

METHODS: MEDLINE and EMBASE searches were supplemented by information from trial registers of randomized controlled trials (RCTs) for GEM-based combination therapy and GEM alone for APCa. A quantitative meta-analysis was carried out by two reviewers based on the inclusion criteria from all available RCTs. The meta-analysis involved overall survival (OS), objective remission rate (ORR), clinical benefit rate (CBR), time to progress/progress free survival (TTP/PFS) and toxicity.

RESULTS: The meta-analysis included 22 RCTs. There was significant improvement in the GEM combination group with regard to the 6-mo survival rate (RD = 0.04, 95% CI 0.01-0.06, P = 0.008), 1-year survival rate (RD = 0.03, 95% CI 0.01-0.05, P = 0.01), ORR (RD = 0.04, 95% CI 0.01-0.07, P = 0.02), CBR (RD = 0.10, 95% CI 0.02-0.17, P = 0.01) and 6-mo TTP/PFS (RD = 0.07, 95% CI 0.04-0.10, P < 0.00001). However, the Grade 3-4 toxicity set by WHO was higher for the GEM combination group for neutropenia (RD = 0.05, 95% CI 0.01-0.10, P = 0.02), thrombocytopenia (RD = 0.05, 95% CI 0.02-0.08, P = 0.002) and vomiting/nausea (RD = 0.03, 95% CI 0.00-0.05, P = 0.02).

CONCLUSION: GEM-based combination therapy may improve the overall survival and palliation in optimal patients with APCa as compared with GEM alone.

Key words: Chemotherapy; Pancreatic cancer; Meta-analysis; Gemcitabine

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INTRODUCTION

Gemcitabine (GEM) monotherapy currently is considered as a standard treatment for patients with advanced pancreatic cancer (APCa). However, patients treated with GEM alone have poor prognoses, and their overall median survival (OS) was only 5.65 mo[1]. Attempts have been made to increase the objective remission rate (ORR) and survival of APCa patients, in particular, by exploring the effects of the combined GEM with other drugs. In many phase Ⅱ studies, GEM combinations have improved ORR and OS. Based on these results, many prospective, randomized phase Ⅲ trials comparing GEM used in combination and alone have been carried out. But these trials had different results and the population enrolled is small. Therefore, the NCCN guidelines (National Comprehensive Cancer Network, v.2.2006) indicate that GEM-based combination therapy may be an optimal treatment for APCa patients with a good performance status, including GEM + cisplatin (DDP), GEM + oxaliplatin, GEM + capecitabine, GEM + erlotinib and so on. But these guidelines were based on low level evidence including clinical experience (category 2A). The role of GEM-based combination therapy for the treatment of APCa is still unclear. We therefore, conducted a systematic review and quantitative meta-analysis to evaluate the available evidence from the relevant randomized trials.

MATERIALS AND METHODS

Literature search

We carried out a comprehensive search of literature

with MEDLINE (1966-2006), EMBASE (1966-2006), CBMdisc (1981-2006), ASCO Abstracts (1995-2005) and EBM Reviews (Cochrane Database of Systematic Reviews 1st Quarter, 2006) ACP Journal Club (1991-2006), (Database of Abstracts of Reviews of Effects 1st Quarter 2006), Cochrane Central Register of Controll ed Trials (1st Quarter, 2006), using the terms: 'pancreas', 'pancreatic cancer', 'pancreatic carcinoma, 'pancreatic adenocarcinoma', 'pancreatic neoplasms', 'gemzar', ' gemcitabine' (no limit to language). Date of last search: April 26, 2006.

Selection criteria

Study design: Trials should be prospective, properly randomized and well designed, which were matched for age, stage, performance status, *etc*.

Study population: Patients with APCa, as well as those with locally advanced, or metastatic disease, were included in the study. Patients eligible for the study were required to have histologically or cytologically proved pancreatic cancer. Furthermore, they should have a baseline Karnofsky performance status of $\geqslant$ 50% (or Eastern Cooperative Oncology Group performance status < 2) and adequate hematological, renal, cardiac and hepatic function. Patients with estimated life expectancy of at least 12 wk, should have received no chemotherapy, radiotherapy and other antitumor therapy in the 6 mo prior to the study entry.

Intervention: The treatment group received GEM-based combination therapy, and the control group received GEM alone.

Outcome: The primary outcome measurement was OS, followed by ORR and toxicity. The follow-up rate should be above 95%.

Data collection and analysis: Two reviewers assessed the abstracts identified from the defined sources. Both reviewers independently selected trials for inclusion according to prior agreement regarding the study population and the intervention. If one of the reviewers concluded an abstract to be eligible, the full text of article was retrieved and reviewed in detail by both reviewers. Missing data from the primary study reports was requested from the investigators. If the same trial appeared on different publications, the final data of the trial was chosen. Methodologic quality of the trials was assessed using a validated scale (range, 0 to 5) applied to items that influence the intervention efficacy. It was reported by Jadad *et al*[2] that the scale consisted of items pertinent to randomization, masking, dropouts, and withdrawals. The following information was obtained from each trial: year of publication, number of patients, performance status, chemotherapy regimen, objective response rate, overall survival, progress free survival, clinical benefit, toxicity, etc. For response assessment, we used trials that included patients with measurable or assessable diseases, and that were analyzed mainly with WHO's criteria. Toxicity profiles were reported according to the WHO's criteria.

Statistical analysis

The primary end point was a 6-mo survival rate after randomization. The other end points were 1-year survival rate, ORR, CBR, 6-mo TTP/PFS rate and adverse effects. All variables were defined as dichotomous data (e.g., 6-mo survival rate used variables as follows: the alive or dead at 6 mo after randomization). We standardized the therapeutic results by obtaining the risk difference (RD) between the GEM combination group and the GEM alone group. Publication bias was examined using a funnel plot[3]. We looked for heterogeneity among the trials based on Cochran's χ^2 test. All analyses were performed strictly with RevMan software (version 8.2, Cochrane). *P* value less than 0.05 was considered as significant in difference.

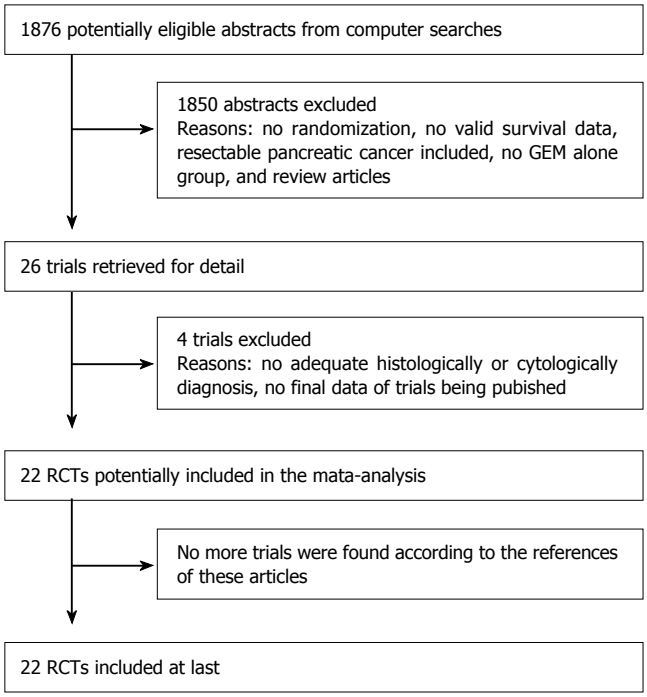

Figure 1 The flow chart. GEM: gemcitabine; RCTs: randomized controlled trials.

RESULTS

Trial flow

The flow chart of our study is shown in Figure 1. Because the trial reported by Degen *et al*[4] involved some patients diagnosed by imageology, we excluded this trial from our analysis. Of the 26 trials, three reported by Ohkawa *et al*[5], Richards *et al*[6], and Shapiro *et al*[7], were excluded because of no final data. Both reviewers finally agreed to include 22 RCTs involving 5473 APCa patients in the meta-analysis.

Characteristics of selected trials

These prospective randomized controlled studies are summarized in Table 1. All selected trials for inclusion strictly according to prior selection criteria, were prospective, randomized and well designed, and the clinical characteristics were matched for age, stage, performance status, and so on. All studies reviewed were considered high in quality, for they achieved a score of 3 or higher in the assessment scale of Jadad's study design. Patients eligible for these studies had histologically or cytologically

Table 1 Randomized controlled trials (GEM combination *vs* GEM alone)

Studies	Intervention	Patients	OS (d)	6-mo survival (%)	1-yr survival (%)	6-mo TTP/PFS/ TTF rate (%)	ORR (CR + PR) %	CBR	Jadad score
Scheithauer 2003[8]	Gem	42	246	59.4	37.2	24.6 (PFS)	6/42	10/30	3
	Gem + Capecitabine	41	285	67.7	31.8	36.9	7/41	15/31	
Colucci 2002[9]	Gem	54	140	31.5	11	18 (TTP)	5/48	21/43	3
	Gem + DDP	53	210	47	11.3	28	14/45	20/38	
Wang XY 2002[10]	Gem	20	-	81.3	31.3	-	1/16	14/16	3
	Gem + DDP	22	-	61.6	11.1	-	2/18	14/20	
Gansauge 2002[11]	Gem	28	144	32	11	-	1/28	-	3
	Gem + NSC-631570	28	279	64	29	-	6/28	-	
Berlin 2002[12]	Gem	162	162	42	15.5	32/160 (PFS)	9/162	-	3
	Gem + 5-FU	160	201	55	21.9	41/158	11/160	-	
Bramhall 2002[13]	Gem + placebo	119	164	43	17	23 (TTF)	14/88	-	5
	Gem + marimastat	120	165.5	47	18	29	11/97	-	
Cutsem 2004[14]	Gem + placebo	347	182	49	24	-	28/347	-	5
		341	193	53	27	-	20/341	-	
Louvet 2005[15]	Gem	156	213	60.4	27.8	27.4 (PFS)	27/156	26.9	3
	Gem[1] + Oxaliplatin	157	270	68	34.7	43	42/157	38.2	
Reilly 2004[16]	Gem	174	186	51	21	27 (TTP)	9/127	-	3
	Gem + DX-8951f	175	201	54	23	39	12/147	-	
Richards 2004[17]	Gem	282	189	50.9	20.1	27.6 (PFS)	20/220	-	3
	Gem + Pemetrexed	283	186	50.9	21.4	32.1	42/230	-	
Li CP 2004[18]	Gem	25	138	20.3	13.6	11.8 (TTP)	3/25	9/25	3
	Gem + DDP	21	168	31.1	6.3	11.8	2/21	6/21	
Reni 2004[19]	Gem	47	-	63.9	21.3	12.9 (PFS)	4/47	5/20	3
	Gem + 5-FU + DDP + EPI	52	-	64.6	38.5	37.4	20/52	15/23	
Viret 2004[20]	Gem	41	201	58.3	25.1	10 (TTF)	2/41	-	3
	Gem + DDP	42	241	55.5	32.4	14	3/42	-	
Rocha Lima 2004[21]	Gem	180	198	52.9	22	21.9 (TTP)	8/180	-	3
	Gem + Irinotecan	180	189	50.7	21	30.6	29/180	-	
Costanzo 2001[22]	Gem	49	217	59	14.5	-	4/48	-	3
	Gem + 5-FU	44	210	59	23.3	-	5/43	-	
Heinemann 2003[23]	Gem	97	180	48.6	22.5	25.6 (TTP)	8/93	-	3
	Gem + DDP	95	228	59.4	27.5	39.3	10/92	-	
Kulke 2004[24]	Gem[2]	45	-	24/45	-	-	-	-	3
	Gem + DDP	45	-	23/45	-	-	-	-	
	Gem + Docetaxel	49	-	22/49	-	-	-	-	
	Gem + Irinotecan	44	-	21/44	-	-	-	-	
Richards 2002[25]	Gem + Placebo	88	213	62.9	20.4	25.9 (TTF)	5/63	-	5
	Gem + CI-994	86	191	60.8	18.5	16.7	1/61	-	
Moore 2005[26]	Gem + Erlotinib	285	191	58	24	32 (PFS)	23/268	-	5
	Gem + placebo	284	177	49	17	25	21/262	-	
Stathopoulos 2005[27]	Gem	70	195	50	21.82	-	7/70	-	3
	Gem + Irinotecan	60	192	60	24.29	-	9/60	-	
Riess 2005[28]	Gem	236	186	53	20	30 (TTP)	17/236	-	3
	Gem + 5-FU/CF	230	175.5	49	20	29	11/230	-	
Herrmann 2005[29]	Gem	157	219	62	27	42 (PFS)	12/152[3]	-	3
	Gem + Capecitabine	159	252	60	31	42	15/148	-	

[1]Gemcitabine 1 g/m^2 as a 100-min infusion; [2]Gemcitabine 1500 mg/m^2 at a fixed dose rate of 10 mg/m^2 per minute; [3]RECIST criteria.

proved pancreatic cancer, with same baseline data and without evidence of selection bias. Of the 22 trials, seven were randomized phase Ⅱ trials, and the others were randomized phase Ⅲ trials. The 6-mo survival rate was extracted from each of the 22 trials, and objective remission rates were recorded in most of the trials. Only a few trials provided CBR, PFS, TTP and TTF (time of treatment failure).

Overall survival

The 5473 randomized patients from 22 RCTs, 2772 in the GEM combination group and 2701 in the GEM alone group, were included in the meta-analysis. The result of the test for heterogeneity of the therapeutic effect was not significant ($P = 0.19$). Therefore, we selected a fixed effect model. There was a significant improvement in 4% of the GEM combination group in 6-mo survival rate (95% CI 0.01-0.06, $P = 0.008$). The results of the meta-analysis in 6-mo survival rate are presented in Figure 2.

With the same technique, 5292 patients from 21 RCTs were analyzed. In the GEM combination group, a 3% improvement was made in 1-year survival rate as compared with the GEM alone group, and this difference being statistically significant (95% CI 0.01-0.05, $P = 0.01$).

The 4912 randomized patients from 21 RCTs, 2461 in the GEM combination group and 2451 in the GEM alone group, were included in the meta-analysis. The result of the test for heterogeneity of the therapeutic effect

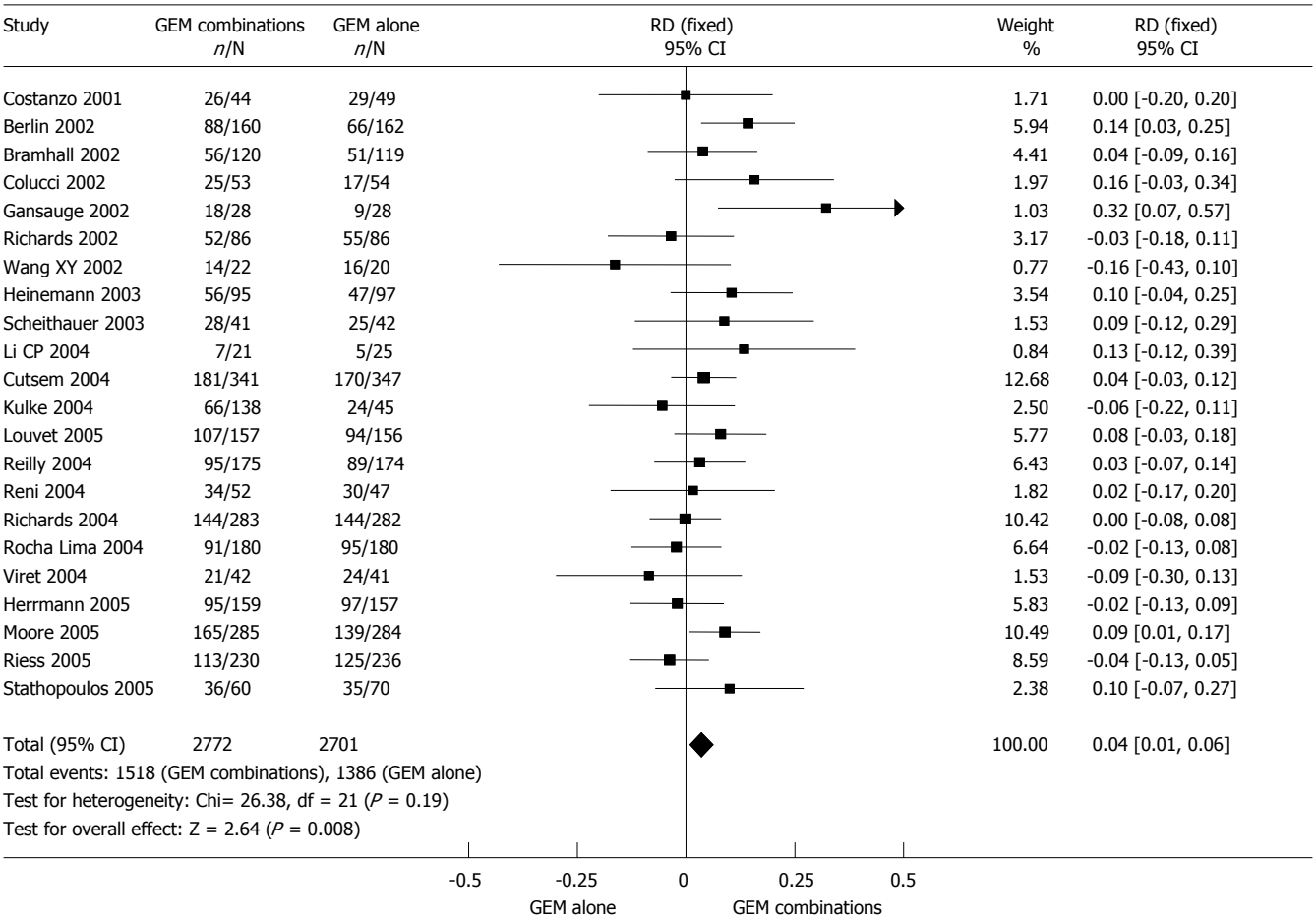

Figure 2 Fixed effect model on RD of 6-mo survival rate.

was significant ($P < 0.0001$). A random effect model was adopted. There was a significant improvement in 4% of the GEM combination group in ORR (95% CI 0.01-0.07, $P = 0.02$). The outcome of the meta-analysis in ORR is presented in Figure 3.

The 580 randomized patients from 6 RCTs, 290 in the GEM combination group and 290 in the GEM alone group, were included in the meta-analysis. The result of the test for heterogeneity of the therapeutic effect was not significant ($P = 0.05$).

A fixed effect model was used. There was a significant improvement in 10% of the GEM combination group in CBR (95% CI 0.02-0.17, $P = 0.01$). The outcome of the meta-analysis in CBR is shown in Figure 4.

Six-month TTP/PFS rate

TTP/PFS was defined as the period from randomization to documented disease progression for TTP or to disease progression or death for PFS. In almost all of the trials, patients recruited with good performance status died of disease progression, so TTP was very close to PFS. Therefore, we can analyze TTP and PFS together.

The 3783 randomized patients from 13 RCTs, 1889 in the GEM combination group and 1894 in the GEM alone group, were included in the meta-analysis. The result of the test for heterogeneity of the therapeutic effect was not significant ($P = 0.20$). A fixed effect model was used. Significant improvement was found in 7% of GEM combination group in 6-mo TTP/PFS rate (95% CI 0.04-0.10, $P < 0.00001$). The meta-analysis in TTP/PFS is presented in Figure 5.

Toxic effects of chemotherapy

Toxic effects of 21 RCTs are summarized in Table 2 (only Grade 3-4 toxic effects were recorded). Main toxic effects were analyzed. Grade 3-4 toxicity was higher in GEM combination group for neutropenia (RD = 5%, 95% CI 0.01-0.10, $P = 0.02$), thrombocytopenia (RD = 5%, 95% CI 0.02-0.08, $P = 0.002$) and vomiting/nausea (RD = 3%, 95% CI 0.00-0.05, $P = 0.02$), all reached significant difference.

Assessment for publication bias

Figures 6 and 7 represent funnel plots that test for publication bias. Funnel plots for the 6-mo survival rate (Figure 6) and 1-year survival rate (Figure 7) supported the lack of evidence for publication bias.

Subgroup analysis

Table 3 shows the subgroup analyses in 6-mo survival rate. It revealed that only the combined chemotherapy consisting of GEM plus a new targeted drug yielded a 6% higher survival rate as compared with chemotherapy of GEM alone.

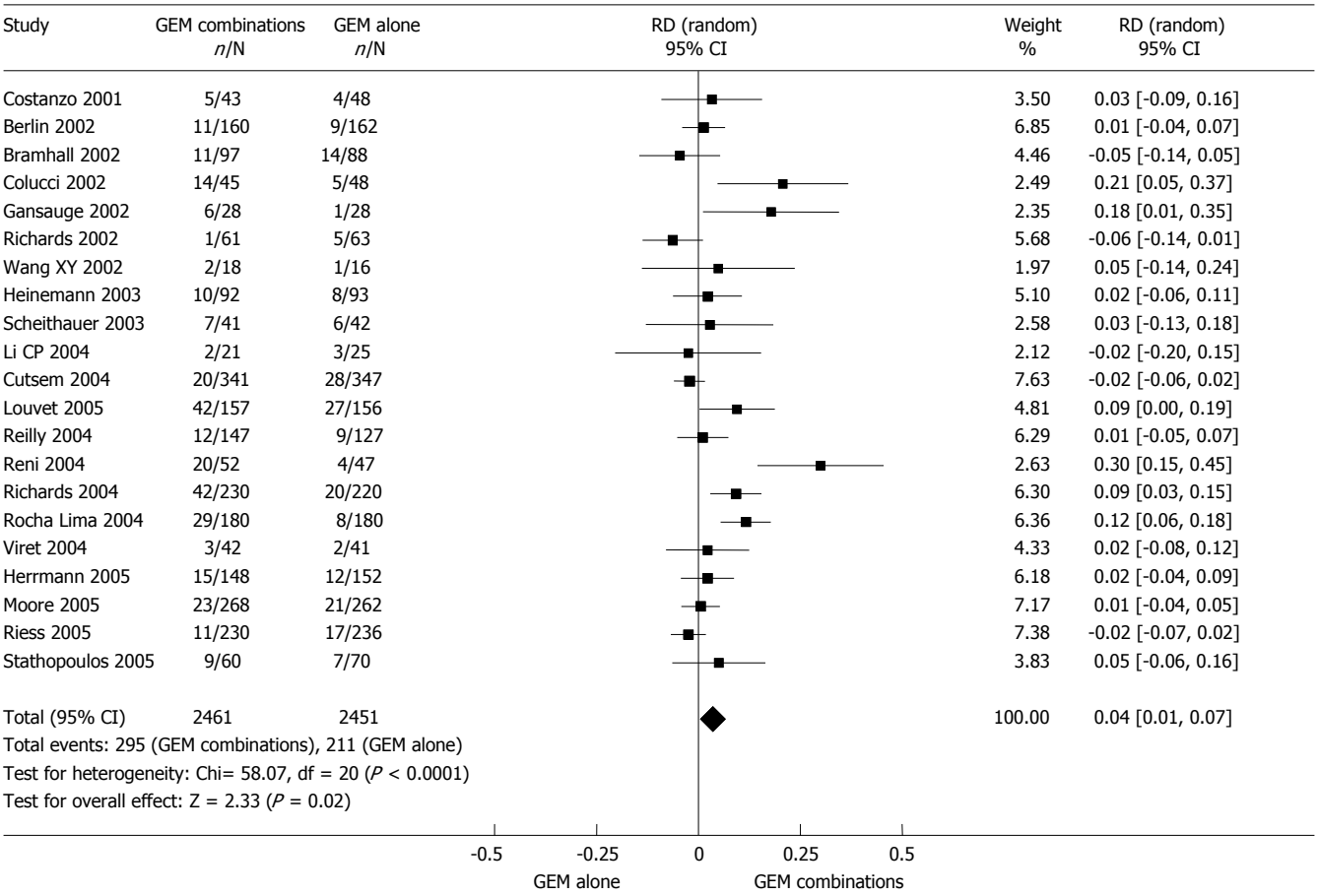

Figure 3 Random effect model on RD of ORR.

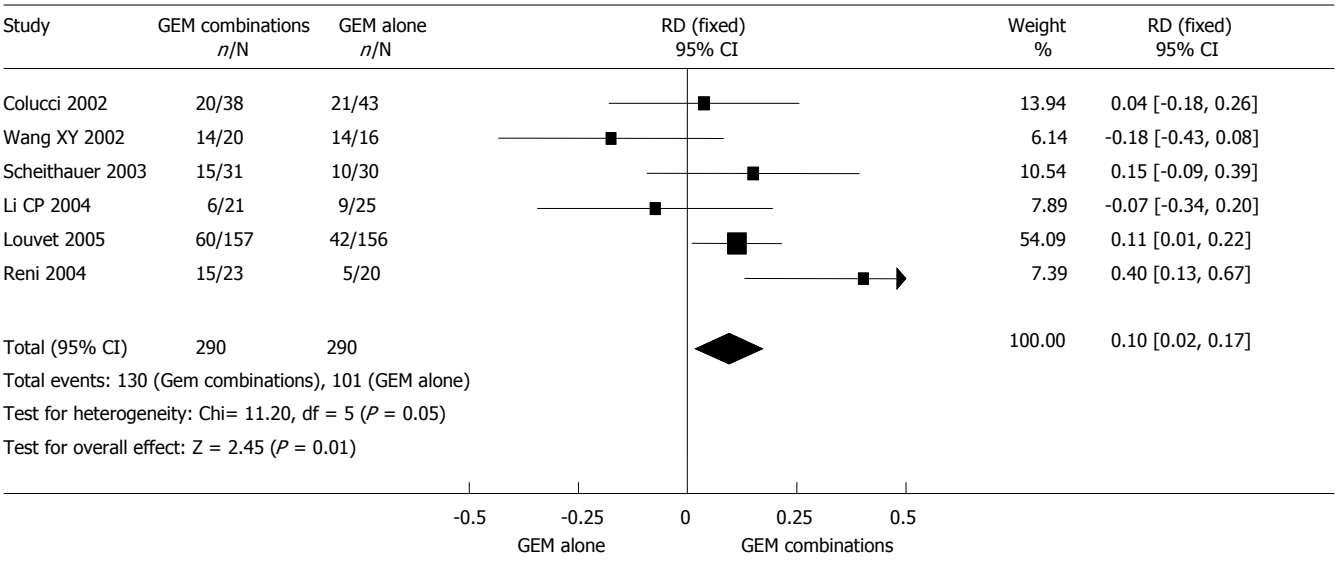

Figure 4 Fixed effect model on RD of CBR.

DISCUSSION

To improve the clinical results of GEM, Phase Ⅱ-Ⅲ trials have been made recently to evaluate the efficacy of combination of GEM with other drugs which were shown to be synergistic *in vitro*, such as 5-fluorouracil (5-FU), DDP, topotecan, *etc*[30,31]. Many trials demonstrated that combined GEM chemotherapy improved ORR and PFS compared with GEM alone, and a few trials reported significant OS advantage (Table 1).

The present meta-analysis shows that GEM combination produced a significant survival advantage as compared with GEM alone in patients with APCa. GEM combination was also found superior to GEM alone in

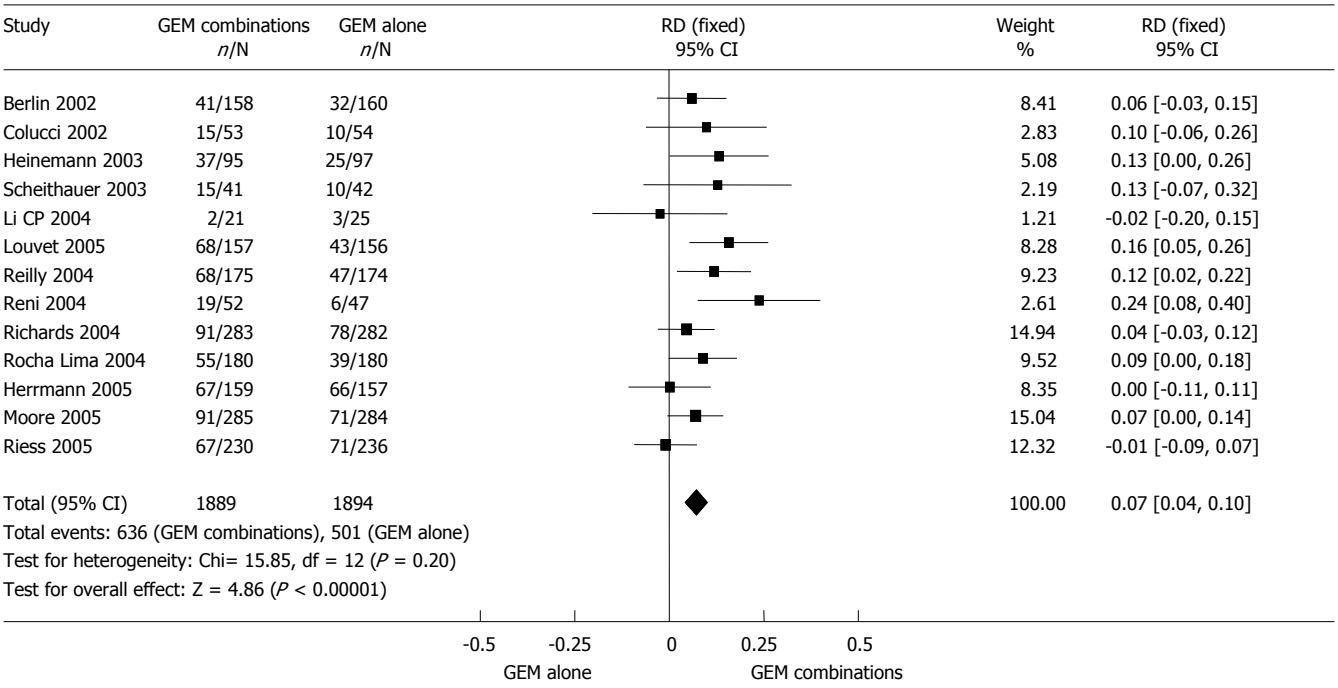

Figure 5 Fixed effect model on RD of 6-mo TTP/PFS rate.

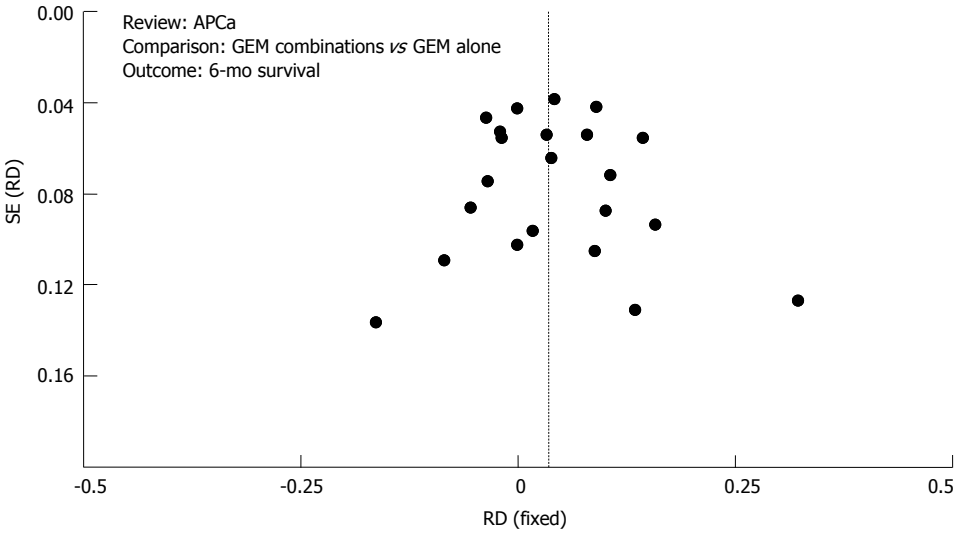

Figure 6 Funnel plots for 6-mo survival rate.

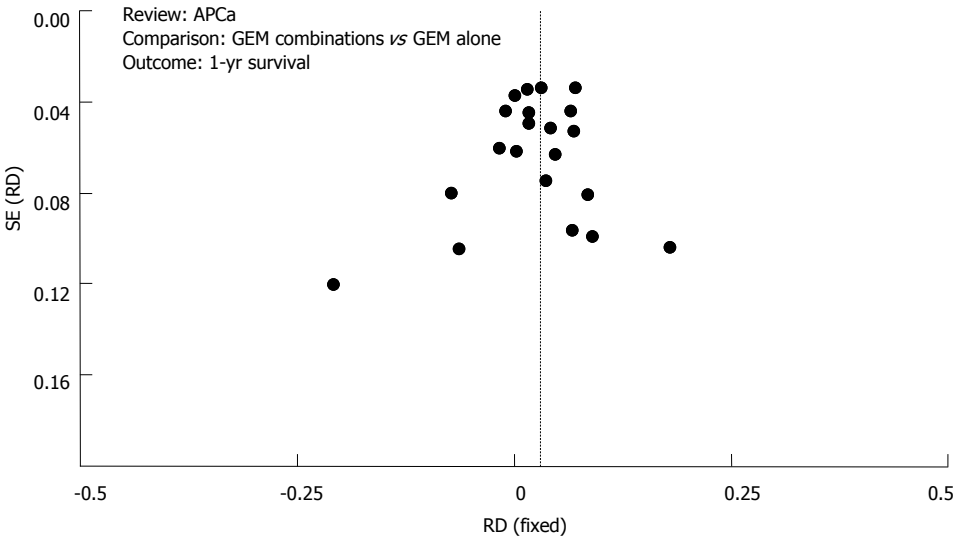

Figure 7 Funnel plots for 1-yr survival rate.

Table 2 Toxic effects recorded from randomized controlled trials (Grade 3-4 toxic effects)

Studies	Intervention	Neutrophils	Platelets	Anemia	Infection	Nausea/vomit	Mucositis	Diarrhea
Scheithauer2003[8]	Gem	3/39	1/39	0	0	0	0	0
	Gem + Capecitabine	4/40	0	2/40	0	0	0	2/40
Colucci 2002[9]	Gem	5/53	1/53	2/53	-	1/53	1/53	0
	Gem + DDP	9/51	1/51	3/51	-	1/51	0	2/51
Wang XY 2002[10]	Gem	5/19	7/19	2/19	-	0	-	-
	Gem + DDP	7/21	8/21	9/21	-	2/21	-	-
Gansauge2002[11]	Gem	-	-	-	-	3/28	-	1/28
	Gem + NSC-631570	-	-	-	-	1/18	-	0
Berlin 2002[12]	Gem	8/158	17/158	16/158	-	30/158	3/158	/158
	Gem + 5-FU	11/158	30/158	16/158	-	29/158	2/158	/158
Bramhall 2002[13]	Gem + placebo	9/119	-	7/119	12/119	16/119	-	-
	Gem + marimastat	3/120	-	3/120	11/120	13/120	-	-
Cutsem 2004[14]	Gem + placebo	103/342	41/342	55/342	-	58/342	-	10/342
	Gem + R115777	132/331	50/331	66/331	-	46/331	-	13/331
Louvet 2005[15]	Gem	2/156	5/156	16/156	-	12/156	-	2/156
	Gem + Oxaliplatin	2/157	22/157	10/157	-	30/157	-	9/157
Reilly 2004[16]	Gem	24/157	7/157	13/157	-	17/157	-	2/157
	Gem + DX-8951f	50/168	28/168	11/168	-	33/168	-	6/168
Richards 2004[17]	Gem	35/273	17/273	8/273	-	18/273	-	2/273
	Gem + Pemetrexed	123/273	49/273	38/273	-	18/273	-	8/273
Li CP 2004[18]	Gem	2/25	1/25	2/25	-	-	-	-
	Gem + DDP	4/21	5/21	2/21	-	-	-	-
Reni 2004[19]	Gem	9/47	1/47	2/47	-	4/47	1/47	-
	Gem + 5-FU + DDP + EPI	22/52	15/52	2/52	-	3/52	2/52	-
Viret 2004[20]	Gem	16/40	5/40	11/40	-	3/40	-	-
	Gem + DDP	23/41	14/41	14/41	-	9/41	-	-
Rocha Lima 2004[21]	Gem	54/169	24/169	22/169	-	31/169	-	3/169
	Gem + Irinotecan	65/173	34/173	27/173	-	53/173	-	33/173
Costanzo 2001[22]	Gem	1/49	0	3/49	-	0	0	0
	Gem + 5-FU	1/41	1/41	3/41	-	1/41	2/41	0
Heinemann 2003[23]	Gem	8/97	10/97	10/97	2/97	6/97	2/97	4/97
	Gem + DDP	10/95	4/95	13/95	1/95	21/95	4/95	3/95
Kulke 2004[24]	Gem	27/58	15/58	6/58	6/58	13/58	-	1/58
	Gem + DDP	29/62	27/62	11/62	2/62	24/62	-	0/62
	Gem + Docetaxel	19/65	7/65	8/65	8/65	10/65	-	5/65
	Gem + Irinotecan	12/60	9/60	4/60	4/60	17/60	-	10/60
Moore2005[26]	Gem + Erlotinib	71/282	28/282	34/282	45/282	20/282	<1	17/282
	Gem + placebo	73/280	34/280	34/280	39/280	20/280	0	6/280
Stathopoulos 2005[27]	Gem	8/70	0/70	2/70	0	1/70	0	2/70
	Gem + Irinotecan	10/60	2/60	2/60	0	1/60	0	2/60
Riess 2005[28]	Gem	27/225	15/225	15/225	19/225	16/225	-	9/225
	Gem + 5-FU/CF	26/220	28/220	18/220	12/220	30/220	-	8/220
Herrmann 2005[29]	Gem	30/153	7/153	9/153	-	5/153	1/153	3/153
	Gem + Capecitabine	34/155	8/155	9/155	-	8/155	0/155	8/155

5-FU: 5-fluororacil; EPI: Epirubicin.

terms of ORR, CBR and 6-mo TTP/PFS. Although most of the selected RCTs showed no significant survival advantage in the GEM combination group, many trials demonstrated slight survival benefit. Physicians should carefully interpret these results when they apply them in clinical practice because GEM combined with other regimens might lead to reversed therapeutic effects.

Straightforward conclusions from the results of this meta-analysis do support the use of GEM combination in patients with APCa, but toxicities from intensive chemotherapy may obliterate the survival benefit of GEM combination. In another meta-analysis, we had reported that the regimens GEM plus DDP were not superior to GEM alone in patients with APCa, which produced more side effects[32]. Furthermore, the subgroup analyses did not show any significant survival advantage in most of GEM combination groups, such as GEM plus 5-FU, GEM plus topoisomerase I inhibitor, and so on. It indicates that not all GEM combined chemotherapy have therapeutic advantage. We suggest that GEM combination, including GEM plus oxaliplatin, and GEM plus erlotinib, should be considered as optimal treatment for patients with APCa. In addition, we found that patients with good perforemance status gained great survival advantage in the sub-group analyses as reported by many other authors[28,29,12]. In our opinion, GEM combination should be applied to patients with good performance status, but carefully to the weak patients.

We found that patients receiving GEM-based combination therapy developed side effects more frequently, including neutropenia, thrombocytopenia and vomiting/nausea , which might lead to a deterioration in

Table 3 Subgroup analyses on 6-mo survival rate

Subgroups	Trials	Patients	Mode	RD [95% CI]	*P*
GEM plus targeted drug *vs* GEM alone	[13, 14, 26]	1496	Fixed	0.06 [0.01, 0.11]	0.02
GEM plus DDP *vs* GEM alone	[9, 10, 18, 20, 23, 24]	560	Fixed	0.05 [-0.03, 0.13]	0.24
GEM plus 5-FU *vs* GEM alone	[12, 22, 28]	881	Random	0.04 [-0.09, 0.17]	0.57
GEM plus topoisomerase I inhibitor *vs* GEM alone	[16, 21, 24, 27]	928	Fixed	0.01 [-0.05, 0.08]	0.72
GEM plus capecitabine *vs* GEM alone	[8, 29]	399	Fixed	0.00 [-0.08, 0.10]	0.97

quality of life (QOL). However, the significant advantage of CBR and TTP/PFS in the GEM combination might be converted to the improvement of QOL**.** Because the primary role of chemotherapy in patients with APCa is palliative, the influence on the QOL of the patients is an important issue in determining the true value of the therapy. However, because the methods for QOL assessment from the included trials were quite different, there was no valid meta-analysis of QOL . We also noted that the CBR analysis was made in only six trials, so the result was still unreliable.

The mata-analysis was based on RCTs with high quality. We carried out a comprehensive search of the literature with barely all of cancer database. Publication bias is frequently cited as a reason for lack of validity in meta-analyses. It could occur if studies finding no association between exposure and disease were less likely to be submitted and accepted for publication than studies finding a positive association. In fact, the results of most of the studies in our meta-analyses were negative, as stated by the authors. The funnel plots also showed no evidence of publication bias. Therefore, our meta-analysis provided a valid assessment and creditable results.

Several technical issues have to be mentioned regarding this meta-analysis. One major limitation is the data source 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, we should interpret the results with care, especially for a positive result. Clearly, further investigations using IPD should be conducted to examine the main end points. 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. Although we applied a random-effect model that takes possible heterogeneity into consideration, there were still many factors causing heterogeneity, such as different drug combination, two infusion methods of gemcitabine and so on.

In conclusion, the meta-analysis indicates that GEM-based combination therapy may improve the overall survival and palliation in optimal patients with APCa as compared with GEM alone. Although the application of GEM combination is still controversial, it is a progressive method from the prospective view of point. At the same time, new regimens of drug administration should be explored in future studies.

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REFERENCES

1 **Burris HA 3rd**, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; **15**: 2403-2413

2 **Jadad AR**, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1-12

3 **Sutton AJ**, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. *BMJ* 2000; **320**: 1574-1577

4 **Degen G,** Hong Z. Treatment effectiveness evaluation of gemcitabine for pancreatic cancer. *Zhonghua Fubu Jibing Zazhi* 2003; **3**: 570-571

5 **Ohkawa S.** Randomized controlled trial of gemcitabine in combination with UFT versus gemcitabine alone in patients with advanced pancreatic cancer. J Clin Oncol 2004; **22**: 4131

6 **Richards DA**, Oettle H, Vervenne WL, Saif MW, Thomas JP, Spitzer G, Visseren-Grul C, Enas N and Weitzman A. Randomized double-blind phase II trial comparing gemcitabine (GEM) plus LY293111 *vs* GEM plus placebo in advanced adenocarcinoma of the pancreas. *J Clin Oncol* 2005; **23**: 4092

7 **Shapiro J**, Marshall J, Karasek P, Figer A, Oettle H, Couture F, Jeziorski K, Broome P and Hawkins R. G17DT+gemcitabine [Gem] versus placebo+Gem in untreated subjects with locally advanced, recurrent, or metastatic adenocarcinoma of the pancreas: Results of a randomized, double-blind, multinational, multicenter study. *J Clin Oncol* 2005; **23**: 4012

8 **Scheithauer W**, Schüll B, Ulrich-Pur H, Schmid K, Raderer M, Haider K, Kwasny W, Depisch D, Schneeweiss B, Lang F, Kornek GV. 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

9 **Colucci G**, Giuliani F, Gebbia V, Biglietto M, Rabitti P, Uomo G, Cigolari S, Testa A, Maiello E, Lopez M. 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**: 902-910

10 **Wang XY**, Ni QX, Jin ML, Li ZS,Wu YX, Zhao YP and Feng FY. Gemcitabine or gemcitabine plus cisplatin for in patients with locally advanced or metastatic pancreatic cancer. *Zhonghua Fubu Jibing Zazhi* 2002; **24**: 404-407

11 **Gansauge F**, Ramadani M, Pressmar J, Gansauge S, Muehling B, Stecker K, Cammerer G, Leder G, Beger HG. NSC-631570

(Ukrain) in the palliative treatment of pancreatic cancer. Results of a phase II trial. *Langenbecks Arch Surg* 2002; **386**: 570-574

12 **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**: 3270-3275

13 **Bramhall SR**, Schulz J, Nemunaitis J, Brown PD, Baillet M, Buckels JA. A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. *Br J Cancer* 2002; **87**: 161-167

14 **Van Cutsem E**, van de Velde H, Karasek P, Oettle H, Vervenne WL, Szawlowski A, Schoffski P, Post S, Verslype C, Neumann H, Safran H, Humblet Y, Perez Ruixo J, Ma Y, Von Hoff D. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. *J Clin Oncol* 2004; **22**: 1430-1438

15 **Louvet C**, Labianca R, Hammel P, Lledo G, Zampino MG, André T, Zaniboni A, Ducreux M, Aitini E, Taïeb J, Faroux R, Lepere C, de Gramont A. 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**: 3509-3516

16 **O'Reilly EM**, Abou-Alfa GK, Letourneau R, Harker WG, Modiano M, Hurwitz H, Tchekmedyian NS, Ackerman J, De Jager RL and Eckhardt SG. A randomized phase III trial of DX-8951f (exatecan mesylate; DX) and gemcitabine (GEM) vs. gemcitabine alone in advanced pancreatic cancer (APC). *J Clin Oncol* 2004; **22**: 4006

17 **Richards DA**, Oettle H, Ramanathan R, Ramanathan RK, Van Laethem J-L, Peeters M, Fuchs M, John W, Arning M and Von Hoff D. A randomized phase III study comparing gemcitabine + pemetrexed versus gemcitabine in patients with locally advanced and metastatic pancreas cancer. *J Clin Oncol* 2004; **22**: 4007

18 **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**: 4144

19 **Reni M**, Cordio S, Passardi A, Panucci MG, Passoni P, Oliani C, Luppi G, Galli L, Nicoletti R and Villa E. Final results of a phase III trial of gemcitabine (G) versus PEFG regimen in stage IVA or metastatic pancreatic adenocarcinoma (PA). *J Clin Oncol* 2004; **22**: 4010

20 **Viret F**, Ychou M, Lepille D, Mineur L, Navarro F, Topart D, Fonck M, Goineau J, Madroszyk-Flandin A and Chouaki N. 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 **Rocha Lima CMS**, Rotche R, Jeffery M, Trudeau M, Cisar L A, Morganti A, Gruia G, Miller L and Green MR. A randomized phase 3 study comparing efficacy and safety of gemcitabine (GEM) and irinotecan (I), to GEM alone in patients (pts) with locally advanced or metastatic pancreatic cancer who have not received prior systemic therapy. *Proc Am Soc Clin Oncol* 2003; **22**: 1005

22 **Di Costanzo F**, Sdrobolini A, Carlini P, Massidda B, Mattioli R, Iop A, Barletta E, Moscetti L, Recchia F, Tralongo P and Ospedaliera S A. Gemcitabine (GEM) Alone or in Combination with 5-FU Continuous Infusion (CI) in the Treatment of Advanced Pancreatic Cancer (APC): a GOIRC Randomized Phase II Trial. *Proc Am Soc Clin Oncol* 2001; **20**: 612

23 **Heinemann V**, Quietzsch D, Gieseler F, Gonnermann M, Schonekas H, Rost A, Neuhaus H, Haag C, Stoffregen C and Clemens M. A phase III trial comparing gemcitabine plus cisplatin vs. gemcitabine alone in advanced pancreatic carcinoma. *Proc Am Soc Clin Oncol* 2003; **22**: 1003

24 **Kulke MH**, Niedzwiecki D, Tempero MA, Hollis DR and 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

25 **Richards DA**, Waterhouse DM, Wagener DJ, Krishnamurthi SS, Rosemurgy A, Dasse KD, Macdonald K, Gulyas S, Plante M, Copley-Merriman C and Grove W. Randomized, double-blind, placebo-controlled phase 2 study of the histone deacetylase inhibitor CI-994 plus gemcitabine (CI-994+G) versus placebo plus gemcitabine (P+G) in the treatment of patients with advanced pancreatic cancer (APC) . *Proc Am Soc Clin Oncol* 2002; **21**: 644

26 **Moore MJ,** Goldstein D, Hamm J, Kotecha J, Gallinger S, Au HJ, Nomikos D, Ding K, Ptaszynski M and Parulekar W. Erlotinib improves survival when added to gemcitabine in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group [NCIC-CTG]. 2005 Gastrointestinal Cancers Symposium: Multidisciplinary Approaches to Gastrointestinal Malignancies and Premalignancies; 2005 January 27-29; Hollywood, FL: Abstract 77

27 **Stathopoulos G**, Aravantinos G, Syrigos K, Kalbakis K, Karvounis N, Papakotoulas P, Boukovinas J, Potamianou A, Polyzos A, Christophillakis C and Georgoulias V. A randomized phase III study of irinotecan/ gemcitabine combination versus gemcitabine in patients with advanced/ metastatic pancreatic cancer. *J Clin Oncol* 2005; **23**: 4106

28 **Riess H**, Helm A, Niedergethmann M, Schmidt-Wolf I, Moik M, Hammer C, Zippel K, Weigang-Köhler K, Stauch M and Oettle H. 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

29 **Herrmann R**, Bodoky G, Ruhstaller T, Glimelius B, Saletti P, Bajetta E, Schueller J, Bernhard J, Dietrich D and Scheithauer W. Gemcitabine (G) plus capecitabine (C) versus G alone in locally advanced or metastatic pancreatic cancer. A randomized phase III study of the Swiss Group for Clinical Cancer Research (SAKK) and the Central European Cooperative Oncology Group (CECOG). *J Clin Oncol* 2005; **23**: 4010

30 **Kanzawa F**, Saijo N. In vitro interaction between gemcitabine and other anticancer drugs using a novel three-dimensional model. *Semin Oncol* 1997; **24**: S7-8-S7-16

31 **Bergman AM**, Ruiz van Haperen VW, Veerman G, Kuiper CM, Peters GJ. Synergistic interaction between cisplatin and gemcitabine *in vitro*. *Clin Cancer Res* 1996; **2**: 521-530

32 **Xie de R**, Liang HL, Wang Y, Guo SS. Meta-analysis of inoperable pancreatic cancer: gemcitabine combined with cisplatin versus gemcitabine alone. *Chin J Dig Dis* 2006; **7**: 49-54

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