Does gemcitabine-based combination therapy improve the prognosis of unresectable pancreatic cancer?

Chen Sun, Daniel Ansari, Roland Andersson, De-Quan Wu

AIM: To assess whether gemcitabine-based combination therapy improves the prognosis of unresectable pancreatic cancer compared with gemcitabine treatment alone.

METHODS: A quantitative up-to-date meta-analysis was undertaken to investigate the efficacy of gemcitabine-based combination treatment compared with gemcitabine monotherapy in locally advanced or metastatic pancreatic cancer. Inclusion was limited to high-quality randomized clinical trials.

RESULTS: Twenty-six studies were included in the present analysis, with a total of 8808 patients recruited. The studies were divided into four subgroups based on the different kinds of cytotoxic agents, including platinum, fluoropyrimidine, camptothecin and targeted agents. Patients treated with gemcitabine monotherapy had significantly lower objective response rate [risk ratio (RR), 0.72; 95% confidence interval (CI): 0.63-0.83; \( P < 0.001 \)], and lower 1-year overall survival (RR, 0.90; 95%CI: 0.82-0.99; \( P = 0.04 \)). Gemcitabine monotherapy caused fewer complications, including fewer grade 3-4 toxicities: including vomiting (RR, 0.75; 95%CI: 0.62-0.89; \( P = 0.001 \)), diarrhea (RR, 0.66; 95%CI: 0.49-0.89; \( P = 0.006 \)), neutropenia (RR, 0.88; 95%CI: 0.72-1.06; \( P = 0.18 \)), anemia (RR, 0.96; 95%CI: 0.82-1.12; \( P = 0.60 \)), and thrombocytopenia (RR, 0.76; 95%CI: 0.60-0.97; \( P = 0.03 \)) compared with gemcitabine combination therapies.

CONCLUSION: Gemcitabine combination therapy provides a modest improvement of survival, but is associated with more toxicity compared with gemcitabine monotherapy.

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Key words: Pancreatic cancer; Gemcitabine; Combination therapy; Outcome; Meta-analysis

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INTRODUCTION

Pancreatic cancer is a highly lethal disease, and represents the fourth cause of cancer-related death in the Western
world. In the United States, the incidence of pancreatic cancer almost equals its mortality, with 43,140 estimated new cases and 36,800 deaths in 2010. Globally, the incidence of new cases is approximately 230,000 each year. Despite advances in diagnosis, staging, and surgical management of the disease during the past decade, the 5-year survival rate in the United States, Europe, and Australia is less than 50%.

Pancatic cancer is characterized by a rapid disease progression and highly invasive tumor phenotype, with most patients having unresectable disease at diagnosis, and chemotherapy being the only possible treatment option for these patients.

Gemcitabine is a pyrimidine antimetabolite and analog of deoxycytidine. It was approved by the Food and Drug Administration as a first-line treatment for patients with locally advanced (stage II or stage III disease when surgery is not an option) or metastatic (stage IV) cancer of the pancreas, and has been widely used during the last decade. However, because of high levels of intrinsic and acquired chemoresistance, a large number of patients do not respond to gemcitabine. To improve clinical efficacy, systemically administered gemcitabine is often combined with a second cytotoxic agent, such as platinum analogs, fluoropyrimidine, or a targeted cytotoxic agent. Numerous clinical trials have aimed at proving the superiority of gemcitabine-based combination therapy over single-agent gemcitabine treatment. However, most of the results of clinical trials have important limitations, including lack of statistical power because of small study populations. Thus, there remain several areas of controversy and uncertainty concerning optimal treatment regimens.

In the present study, we undertook a comprehensive up-to-date meta-analysis to investigate the efficacy of gemcitabine-based combination treatment in locally advanced or metastatic pancreatic cancer. The aim of this study was to assess whether gemcitabine-based combination therapy improves the prognosis compared with gemcitabine treatment alone and to discuss possible mechanisms.

MATERIALS AND METHODS

Literature search strategy

We carried out a comprehensive search of the literature, including PUBMED (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (http://www.embase.com/home), American Society of Clinical Oncology abstracts (http://www.asco.org), and the Cochrane Database (http://www.thecochranelibrary.com). The following keywords were used in the search: (“Gemcitabine” or “Gemzar”), and (“pancreatic cancer” or “pancreatic tumor” or “pancreatic carcinoma”), and (“clinical trial”). The deadline for a publication to be eligible for this study was November 5, 2011. In addition to the online search, references from reviews and original articles were also scanned manually to identify further trials that met the eligibility criteria. No language restrictions were applied.

Inclusion and exclusion criteria

Studies included in the analysis had to meet all of the following criteria: (1) prospective, randomized, controlled open or blinded trial; (2) patients with histologically confirmed locally advanced or metastatic pancreatic ductal adenocarcinoma; and (3) assessment of the efficacy of gemcitabine combination therapy vs gemcitabine alone. Non-randomized trials and quasi-randomized trials, studies of curatively aimed resection, and studies where patients had multiple cancers, were excluded to avoid clinical heterogeneities between different studies.

Data extraction and quality assessment

Data extraction and quality assessment were performed independently by two reviewers (CS and DA). Any disagreements between the reviewers were discussed with a third reviewer (RA) to achieve a consensus. The data extracted from the eligible studies included: first author, year of publication, patient characteristics, intervention, and clinical outcome (toxicity, response rate, overall survival and progression-free survival). If the same trial appeared on sequential or multiple publications, the data from the most recent or comprehensive one was included.

The methodological quality of included studies was assessed using the “Jadad scale” or “Oxford quality scoring system.” This tool is an evidence-based quality assessment tool. There are three items (randomization, double blinding, withdrawals and dropouts) directly related to bias reduction for assessment. Each item is given a score of 1 point for each “yes” or 0 points for each “no”, and 1 additional point for appropriate randomization and double blinding. Every eligible study were assessed and given a score from 0-5.

Data analysis

The outcome measures were objective response rate [objective response rate (ORR) = complete response (CR) + partial response (PR)], as previously defined, 1-year overall survival (OS), median progression-free survival (PFS), median OS and toxicity. The analysis of ORR
Table 1 Characteristics of selected trials

| Ref.       | Intervention | n  | Male (%) | Age (range) | Metastatic (%) | Median PFS (mo) | 1-yr OS | Median OS (mo) | Quality |
|------------|--------------|----|----------|-------------|----------------|----------------|---------|----------------|---------|
| Louvet et al[29] | Gem + Oxaliplatin | 163 | 53 | 60.1 (22-75) | 70 | 17.3 | 3.7 | 27.8 | 7.1 | 4 |
| Poplin et al[31] | Gem + Capeitabine | 275 | 56.4 | 64 (31-88) | 90.2 | 6 | 2.6 | 16 | 4.9 | 4 |
| Heinemann et al[37] | Gem + Cisplatin | 95 | 65.3 | 64 (37-82) | 80 | 11.5 | 5.3 | 25.3 | 7.5 |
| Colucci et al[40] | Gem + Capeitabine | 54 | 50 | 63 (43-75) | 65 | 9.2 | 2 | 11 | 5 | 4 |
| Kulke et al[36] | Gem + Cisplatin | 64 | 66 | 58.3 (29-81) | 100 | 13 | 4.5 | NR | 6.7 |
| Berlin et al[25] | Gem + irinotecan | 162 | 53.7 | 64.3 (33-85) | 90.1 | 5.6 | 2.2 | NR | 5.4 | 4 |
| Herrmann et al[34,36] | Gem + Capectabine | 159 | 53 | 62 (36-84) | 79 | 8 | 3.9 | 30 | 7.2 | 4 |
| Cunningham et al[36] | Gem + Capeitabine | 266 | 58 | 62 (26-83) | 71 | 12.4 | 3.8 | 22.0 | 6.2 | 4 |
| Costanzo et al[29] | Gem + irinotecan | 49 | 48 | 64 (34-75) | 73 | 8 | 3.5 | 18 | 7.7 | 4 |
| Abou-Alfa et al[27] | Gem + irinotecan | 174 | 57 | 62.3 (30-84) | 78 | 5.7 | 3.8 | 21 | 6.2 | 4 |
| Stathopoulos et al[36] | Gem + irinotecan | 74 | 42 | 64 (44-83) | 66 | 10 | 2.9 | 21.8 | 6.5 | 4 |
| Lima et al[29] | Gem + irinotecan | 180 | 53.3 | 60.2 (32-82) | 80.6 | 4.4 | 3.0 | 22 | 6.6 | 4 |
| Moore et al[29] | Gem + Erlotinib | 284 | 57 | 64 (36-1-92) | 75.0 | 8.0 | 3.55 | 17 | 5.9 | 4 |
| Cutsem et al[34] | Gem + Tipifarnib | 347 | 58 | 62 (30-88) | 77 | 8 | 3.6 | 24 | 6.0 | 4 |
| Eckhardt et al[38] | Gem + Tipifarnib | 120 | 59 | 60 (35-86) | 73 | NR | 3.05 | NR | 7.36 | 5 |
| Philip et al[27] | Gem + cetuximab | 371 | 54 | 64.3 | 78 | 7 | 3.0 | NR | 5.9 | 4 |
| Kindler et al[29] | Gem + Bevacizumab | 300 | 51 | 65.0 (35-86) | 85 | 10 | 2.9 | NR | 5.9 | 4 |
| Kindler et al[29] | Gem + Asitinitib | 316 | 59 | 62 (35-89) | 72 | 1.6 | 4.4 | NR | 8.5 | 3 |
| Spano et al[32] | Gem + Asitinitib | 34 | 47 | 61.0 (26-78) | 19 | 3 | 3.7 | 23.5 | 5.6 | 4 |
| Friess et al[36] | Gem + Cilengitide | 46 | 37 | 68 (40-80) | 40 | 7 | 4.2 | 36.8 | 6.9 |
| Richards et al[36] | Gem + Enzastarin | 44 | 72.7 | 64 (1-48) | 86.4 | 5.3 | 3.0 | 17 | 5.1 | 4 |
| Bramhall et al[39] | Gem + Marinastat | 119 | 71 | 62 (37-85) | 62 | 16 | 3.2 | 17 | 5.46 | 5 |
| Richards et al[32] | Gem + CA-994 | 85 | 60.2 | 65 (36-83) | 83.0 | 20.1 | 19 | 6.47 | 5 |
| Oettle et al[47] | Gem + F Hemetrexed | 282 | 53.5 | 63 (28-82) | 91.1 | 7.1 | 3.4 | 20.1 | 6.3 | 4 |

NR: No record; PFS: Progression-free survival; OS: Overall survival.

(number of partial and complete responses, as defined by Response Evaluation Criteria in Solid Tumors[16], PFS (time from randomization to progression or death) and OS (time from the date of random assignment until date of death or date last known to be alive) were based on the intent-to-treat population, consisting of all patients randomly assigned onto every study. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, and based on the safety population. The median PFS and median OS were assessed using the paired t-test. P < 0.05 was considered statistically significant.

Meta-analysis was performed using the Review Manager (version 5.1, provided by the Cochrane Collaboration). The strength of the associations between treatment and outcomes were estimated by risk ratio (RR, a ratio...
of the probability of the event occurring in the exposed group versus a non-exposed group) and 95% confidence interval (CI)[13]. The heterogeneities between different studies or different subgroups were estimated using Cochrane's $Q$ test[12,13]. In addition, the $I^2$ value was used for evaluating the extent of heterogeneity between studies or subgroups[14]. The $I^2$ index measures the extent of true heterogeneity dividing the difference between the result of the $Q$ test and its degrees of freedom by the $Q$ value itself, and multiplied by 100. $I^2$ indicated the possibility of the variability among effect sizes caused by true heterogeneity between studies, not by sampling error[14]. If a significant $Q$ test ($P < 0.1$) or $I^2 > 50\%$ indicated that heterogeneity existed between studies, the random effects model was used for meta-analysis, otherwise the fixed effects model was used. Publication bias was assessed by visual inspection of funnel plots.

**RESULTS**

**Literature search and trial flow**

The results of the literature search are depicted in Figure

| Ref. | Intervention | Vomiting | Diarrhea | Neutropenia | Anemia | Thrombocytopenia |
|------|--------------|----------|----------|-------------|--------|-----------------|
| Louvet et al[21] | Gem | 3.2 | 1.3 | 27.6 | 10.3 | 3.2 |
| | Gem + Oxaliplatin | 8.9 | 5.7 | 20.4 | 6.4 | 14.0 |
| Poplin et al[22] | Gem | 7 | 4 | 33 | 10 | 13 |
| | Gem + Oxaliplatin | 16 | 6 | 22 | 6 | 11 |
| Heinemann et al[23] | Gem | 5.9 | 4.7 | NR | 10.6 | 10.6 |
| Colucci et al[24] | Gem + Cisplatin | 22.2 | 3.3 | NR | 13.3 | 4.4 |
| | Gem | 2 | 0 | 9 | 4 | 2 |
| Colucci et al[25] | Gem + Cisplatin | 2 | 4 | 18 | 6 | 2 |
| | Gem | < 1 | 1.5 | 13.7 | 1 | 18.9 |
| Kulke et al[26] | Gem | 24.1 | NR | 82.8 | 20 | 43.1 |
| | Gem + Cisplatin | 29 | NR | 74.2 | 25.8 | 79 |
| | Gem + Irinotecan | 16.7 | NR | 41.7 | 8.3 | 23.3 |
| Berlin et al[27] | Gem | 8 | NR | 5 | 10 | 11 |
| | Gem + 5-fluorouracil | 7 | NR | 7 | 10 | 19 |
| Herrmann et al[28,29] | Gem | 4 | 2 | 19 | 6 | 8 |
| | Gem + Capeitabine | 4 | 5 | 23 | 8 | 4 |
| Cunningham et al[30] | Gem | 6 | 4 | 22 | 6 | 6 |
| | Gem + Capeitabine | 6 | 5 | 35 | 4 | 11 |
| Scheithauer et al[31] | Gem | 0 | 0 | 7.6 | 0 | 2.5 |
| | Gem + Capeitabine | 0 | 5 | 10 | 5 | 0 |
| Costanzo et al[32] | Gem | 0 | 0 | 2 | 7 | 2 |
| | Gem + 5-fluorouracil | 2 | 0 | 2 | 7 | 2 |
| Abou-Alfa et al[33] | Gem | 3.1 | < 1 | 14.6 | 7.6 | 4.4 |
| | Gem + Etsacitabine | 5.3 | 1.1 | 30.3 | 5.9 | 15.4 |
| Stathopoulos et al[34] | Gem | 1.4 | 2.8 | 15.7 | 4.2 | 0 |
| | Gem + Irinotecan | 1.6 | 3.2 | 26.6 | 5 | 5 |
| Lima et al[35,36] | Gem | 8.2 | 1.8 | 31.9 | 13 | 14.2 |
| | Gem + Irinotecan | 13.9 | 18.5 | 37.6 | 16.2 | 19.6 |
| Moore et al[37] | Gem | NR | < 1 | 27% | NR | 11% |
| | Gem + Erlotinib | NR | 2 | 24% | NR | 10% |
| Cutsem et al[38] | Gem | 9 | 3 | 30 | 16 | 12 |
| | Gem + Pemetraxe | 7 | 4 | 40 | 20 | 15 |
| Eckhardt et al[39] | Gem | 9.3 | 0 | 33.9 | 11 | 15.3 |
| | Gem + Pemetraxe | 4 | 0 | 35.5 | 12.1 | 16.1 |
| Philip et al[40] | Gem | 2.2 | 2.5 | 23.9 | 6.2 | 8.5 |
| | Gem + Capeitabine | 6.6 | 2.8 | 23.3 | 9.7 | 6.6 |
| Kindler et al[41] | Gem | NR | 29 | 8 | 12 |
| | Gem + Bevacizumab | NR | 33 | 5 | 12 |
| Kindler et al[42] | Gem | 3.2 | 1.6 | < 1 | < 1 | < 1 |
| | Gem + Axitinib | 3.9 | 1.3 | 0 | 0 | 0 |
| Spano et al[43] | Gem | 10 | 0 | 33 | 17 | 13 |
| | Gem + Axitinib | 6 | 6 | 28 | 8 | 20 |
| Richards et al[44] | Gem | 0 | 2.6 | 28.2 | 5.1 | 25.6 |
| | Gem + Etsacitabine | 2.4 | 3.7 | 18.3 | 3.7 | 14.6 |
| Bramhall et al[45] | Gem | 14% | NR | NR | 7% | NR |
| | Gem + Marimastat | 6% | NR | NR | 3% | NR |
| Richards et al[46] | Gem | 9 | 3 | NR | 5 | 11 |
| | Gem + CA-994 | 9 | 5 | NR | 13 | 25 |
| Oettle et al[47] | Gem | 3.7 | 0.7 | 12.8 | 2.9 | 6.2 |
| | Gem + Pemetraxe | 3.3 | 2.9 | 45.1 | 13.9 | 17.9 |

NR: No record.
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| Study or subgroup | Monotherapy | Combination | Weight (%) | Risk ratio M-H, fixed, 95%CI | Risk ratio M-H, fixed, 95%CI |
|------------------|-------------|-------------|------------|-----------------------------|-----------------------------|
|                  | Events      | Total       | Events     | Total                       |                             |
| 1.1.1 Gem vs gem + platinum |             |             |             |                             |                             |
| Colucci et al[21] | 5           | 54          | 14         | 53                         | 3.0 (0.14, 0.90)            |
| Colucci et al[22] | 20          | 199         | 26         | 201                        | 5.5 (0.45, 1.35)            |
| Heinemann et al[23] | 8           | 89          | 10         | 87                         | 2.2 (0.32, 1.89)            |
| Kulke et al[24] | 6           | 43          | 7          | 56                         | 1.3 (0.40, 3.08)            |
| Louvet et al[25] | 27          | 156         | 42         | 157                        | 8.9 (0.42, 0.99)            |
| Poplin et al[26] | 17          | 275         | 26         | 272                        | 5.6 (0.36, 1.16)            |
| Subtotal (95%CI) | 816         | 826         |            |                            |                             |
| Total events     | 83          | 125         |            |                            |                             |
| Heterogeneity: $\chi^2 = 3.20$, df = 5 ($P = 0.67$); $I^2 = 0\%$ |
| Test for overall effect: $Z = 3.01$ ($P = 0.003$) |
| 1.1.2 Gem vs gem + fluoropyrimidine |             |             |             |                             |                             |
| Berlin et al[27] | 9           | 162         | 11         | 150                        | 2.4 (0.81 (0.34, 1.90) |
| Costanzo et al[28] | 4           | 48          | 5          | 43                         | 1.1 (0.72 (0.21, 2.50) |
| Cunningham et al[29] | 33         | 266         | 51         | 267                        | 10.8 (0.65 (0.43, 0.97) |
| Herrmann et al[30-32] | 12         | 153         | 15         | 150                        | 3.2 (0.78 (0.38, 1.62) |
| Schelthauer et al[33] | 6          | 42          | 7          | 41                         | 1.5 (0.84 (0.31, 2.28) |
| Subtotal (95%CI) | 671         | 661         |            |                            |                             |
| Total events     | 64          | 89          |            |                            |                             |
| Heterogeneity: $\chi^2 = 0.45$, df = 4 ($P = 0.98$); $I^2 = 0\%$ |
| Test for overall effect: $Z = 2.23$ ($P = 0.03$) |
| 1.1.3 Gem vs gem + camptothecin |             |             |             |                             |                             |
| Abou-Alfa et al[34] | 9           | 157         | 12         | 168                        | 2.5 (0.80 (0.35, 1.85) |
| Kulke et al[35] | 6           | 43          | 7          | 51                         | 1.4 (1.02 (0.37, 2.80) |
| Lima et al[36] | 8           | 180         | 29         | 180                        | 6.2 (0.28 (0.13, 0.59) |
| Stathopoulos et al[37] | 7          | 70          | 9          | 60                         | 2.1 (0.67 (0.26, 1.68) |
| Subtotal (95%CI) | 450         | 459         |            |                            |                             |
| Total events     | 30          | 57          |            |                            |                             |
| Heterogeneity: $\chi^2 = 5.63$, df = 3 ($P = 0.13$); $I^2 = 47\%$ |
| Test for overall effect: $Z = 2.92$ ($P = 0.003$) |
| 1.1.4 Gem vs gem + targeted agent |             |             |             |                             |                             |
| Bramhall et al[38] | 14          | 88          | 11         | 97                         | 2.2 (1.40 (0.67, 2.93) |
| Cutsem et al[39] | 28          | 347         | 20         | 341                        | 4.3 (1.38 (0.79, 2.39) |
| Fries et al[40] | 6           | 43          | 8          | 46                         | 1.6 (0.80 (0.30, 2.12) |
| Kindler et al[41] | 30          | 300         | 39         | 302                        | 8.3 (0.77 (0.49, 1.21) |
| Kindler et al[42] | 4           | 255         | 12         | 247                        | 2.6 (0.32 (0.11, 0.99) |
| Moore et al[43] | 23          | 284         | 24         | 285                        | 5.1 (0.96 (0.56, 1.66) |
| Oettle et al[44] | 20          | 282         | 42         | 283                        | 8.9 (0.48 (0.29, 0.79) |
| Philip et al[45] | 23          | 331         | 28         | 329                        | 6.0 (0.82 (0.48, 1.39) |
| Richards et al[46] | 10         | 85          | 8          | 85                         | 1.7 (1.25 (0.52, 3.01) |
| Richards et al[47] | 2          | 44          | 7          | 86                         | 1.0 (0.56 (0.12, 2.58) |
| Spano et al[48] | 1           | 5           | 5          | 9                          | 0.7 (0.41 (0.05, 3.34) |
| Subtotal (95%CI) | 2093        | 2170        |            |                            |                             |
| Total events     | 161         | 204         |            |                            |                             |
| Heterogeneity: $\chi^2 = 14.40$, df = 10 ($P = 0.16$); $I^2 = 31\%$ |
| Test for overall effect: $Z = 2.02$ ($P = 0.04$) |
| Total (95%CI)    | 4030        | 4116        | 100.0      | 0.72 (0.63, 0.83)          |                             |
| Total events     | 338         | 475         |            |                            |                             |
| Heterogeneity: $\chi^2 = 26.81$, df = 25 ($P = 0.37$); $I^2 = 7\%$ |
| Test for overall effect: $Z = 4.80$ ($P < 0.00001$) |
| Test for subgroup differences: $\chi^2 = 3.71$, df = 3 ($P = 0.29$); $I^2 = 19.2\%$ |

Figure 2  Fixed effect model of risk ratio of objective response rate. CI: Confidence interval.

1. Some 2707 studies were initially retrieved. After reading the title and abstract, 2675 studies were excluded, and 32 studies were left for further review. Six of these were excluded because of poor quality or failure to meet the inclusion criteria.

Characteristics of selected trials

The characteristics of the included studies are shown in Table 1. Twenty-six studies were included in the present analysis, with 8808 recruited patients. The studies were divided into four subgroups based on types of cytotoxic agents used, including platinum,[21-28] fluoropyrimidine,[30-41] camptothecin,[21,27,28] and targeted agents.[30-41] All included studies enrolled patients that were ≥ 18 years; had a histologically confirmed locally advanced or metastatic pancreatic cancer not amenable to surgical resection; no previous chemotherapy; a life expectancy of at least 12 wk; a Karnofsky performance status ≥ 50, or World Health Organization performance status of 0-2; and adequate liver, renal, and hematopoietic functions.

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Gemcitabine combination therapy improves objective response rate compared with gemcitabine treatment alone

This analysis evaluated 26 trials (8146 patients) comparing gemcitabine monotherapy with the combination of gemcitabine and some other cytotoxic agent. Based on all studies, patients treated with gemcitabine monotherapy had a significantly lower ORR than gemcitabine combination therapy (RR, 0.72; 95%CI: 0.63–0.83; P < 0.001). The RRs in the different subgroups were 0.67, 0.71, 0.53 and 0.82, for platinum, fluoropyrimidine, camptothecin and targeted agents, respectively. All RRs in the subgroups were also significant. Data are shown in Figure 2.

Gemcitabine combination therapy improves 1-year overall survival rate compared with gemcitabine alone

5717 patients from 18 trials were included in this meta-analysis comparing gemcitabine monotherapy with combination therapies for 1-year overall survival. The RRs of 1-year overall survival were analyzed both totally and in the different subgroups. Subgroup analysis showed that the RRs of the monotherapy-based 1-year overall survival were lower than for the combination groups (RR: 

![Figure 3](www.wjgnet.com) Fixed effect model of risk ratio of 1-year overall survival rate. CI: Confidence interval.
0.91, 0.95, 0.97 and 0.85, for platinum, fluoropyrimidine, camptothecin and targeted agents, respectively, but no significant differences were found. When analyzed in terms of total events, the RR shown in Figure 3 was 0.90 [95%CI: 0.82-0.99]; \( P = 0.04 \). The result showed that the 1-year overall survival rate of gemcitabine monotherapy was almost 90% of that of the combination therapy.

**Gemcitabine combination therapy increases the toxicity effect compared with gemcitabine alone**

Outcomes of the meta-analysis of the main toxicities are presented in Figures 4-8. All RRs with grade 3-4 toxicities analyzed in this study were lower in the gemcitabine monotherapy group than in the combination group. The incidence of vomiting (RR, 0.75; 95%CI: 0.62-0.89; \( P = 0.001 \)), diarrhea (RR, 0.66; 95%CI: 0.49-0.89; \( P = 0.006 \)) and thrombocytopenia (RR, 0.76; 95%CI: 0.60-0.97; \( P = 0.03 \)) were all significantly different between the treatment groups, while no significant difference was noted regarding neutropenia (RR, 0.88; 95%CI: 0.72-1.06; \( P = 0.18 \)) and anemia (RR, 0.96; 95%CI: 0.82-1.12; \( P = 0.60 \)).

In subgroup analysis, the RRs were 0.46-0.98 for vomiting, 0.65-0.70 for diarrhea, 0.70-1.03 for neutropenia, 0.87-1.09 for anemia and 0.65-0.85 for thrombocy-
Table 1. Risk Ratio of Grade 3 or 4 Diarrhea

| Study or subgroup | Monotherapy | Combination | Total events | Test for overall effect: Z = 1.53 (P = 0.13) | Subtotal (95%CI) | Test for subgroup differences: χ² = 11.63, df = 17 (P = 0.002) | Test for subgroup differences: χ² = 0.01, df = 3 (P = 1.00); I² = 0% | Test for subgroup differences: χ² = 11.63, df = 17 (P = 0.82); I² = 0% | Test for subgroup differences: χ² = 0.01, df = 3 (P = 1.00); I² = 0% |
|-------------------|-------------|-------------|--------------|---------------------------------------------|-----------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|
| 1.4.1 Gem vs gem + platinum | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) |
| Colucci et al[41] | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) |
| Colucci et al[41] | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) |
| Heinemann et al[37] | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) |
| Louvet et al[38] | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) |
| Poplin et al[39] | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) |
| Subtotal (95%CI) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) | 0.20 (0.01, 4.00) |

Figure 5. Fixed effect model of risk ratio of grade 3 or 4 diarrhea. CI: Confidence interval.

toopenia, respectively. No subgroup differences in overall toxic outcomes, except for vomiting, were found between the gemcitabine monotherapy group and the combination groups. Gemcitabine monotherapy decreased the incidence rate of vomiting by more than 50% compared with the gemcitabine plus platinum subgroup (RR, 0.46; 95%CI: 0.33-0.64; P < 0.001), while no significant differences for other subgroups was seen. In addition, the results showed that gemcitabine plus fluoropyrimidinide therapy significantly increased the incidence of neutropenia (RR, 0.70; 95%CI: 0.55-0.88; P = 0.002).

The median PFS and median OS between gemcitabine monotherapy and combination therapies

The data of median PFS and OS in every study were extracted and assessed by a paired t-test. The results showed that only gemcitabine plus fluoropyrimidinide significantly increased the median PFS (3.480 vs 4.520; P = 0.045) and median OS (6.950 vs 7.840; P = 0.038). Data are shown in Figure 9.

Publication bias

The funnel plots are shown in Figure 10. There was no
Pancreatic cancer is a devastating disease with a dismal prognosis. Most of patients present with locally advanced or metastatic disease and are thus not candidates for surgical resection, thereby having to rely on palliative chemotherapy as the only treatment option. In this situation, the goals of chemotherapy should be to control tumor progression, decrease toxicity, and improve the survival rate. At present, gemcitabine monotherapy remains the standard treatment for patients with locally advanced or metastatic pancreatic cancer, but its efficacy is unsatisfactory. During the last decade, several randomized controlled clinical trials have evaluated gemcitabine in combination with various agents in an attempt to improve the prognosis of pancreatic cancer. The aim of this meta-analysis was to compare the therapeutic efficacy of gemcitabine-based combination treatments with gemcitabine alone in patients with locally advanced or metastatic pancreatic cancer. The results of this study showed that various combination therapies overall did not provide any major benefit compared with gemcitabine monotherapy. Moreover, gemcitabine monotherapy had an almost 30% lower ORR than combination therapy regimens, but
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only had a 10% lower 1-year OS than combination therapy. According to the present data, 1-year OS in advanced or metastatic pancreatic cancer was low (less than 20%) after gemcitabine monotherapy; therefore, the combination therapy options studied did not improve outcome in a substantial way, the prognosis still being poor.

In addition, there were no significant improvements found in this analysis in median PFS and median OS after combination therapy, except for gemcitabine plus fluoropyrimidine treatment. Our results are similar to previously published analyses [21,31,42]. We also assessed the five most common toxicities related to chemotherapeutic treatment of locally advanced or metastatic pancreatic cancer, including hematological and gastrointestinal side effects. Grade 3-4 toxicities tended to be higher following combination therapy compared with monotherapy, and three of the five investigated toxicities reached significant differences. The RRs of vomiting, diarrhea, and thrombocytopenia in the monotherapy group were about 70% of that noted in the combination therapy group. Furthermore, subgroup analysis showed that the RR of vomiting after treatment with gemcitabine plus platinum was twice that of monotherapy. The results presented here showed that combination therapy induced

| Study or subgroup | Monotherapy | Combination | Risk ratio | Risk ratio |
|------------------|-------------|-------------|------------|------------|
|                  | Events      | Total       | Events     | Total       | Weight (%)| M-H, fixed, 95%CI | M-H, fixed, 95%CI |
| 1.6.1 Gem vs gem + platinum |             |             |             |             |           |             |             |
| Colucci et al [37] | 2          | 54          | 3          | 53          | 1.0       | 0.65 (0.11, 3.76) |             |
| Colucci et al [38] | 2          | 189         | 9          | 186         | 3.0       | 0.22 (0.05, 1.00) |             |
| Heinemann et al [39] | 9         | 85          | 12         | 90          | 3.9       | 0.79 (0.35, 1.79) |             |
| Kulke et al [40] | 12         | 58          | 16         | 62          | 5.2       | 0.80 (0.42, 1.55) |             |
| Louvet et al [41] | 16         | 156         | 10         | 157         | 3.3       | 1.61 (0.75, 3.44) |             |
| Poplin et al [42] | 26         | 264         | 16         | 263         | 5.3       | 1.62 (0.89, 2.95) |             |
| Subtotal (95%CI) | 806        | 811         |            |             | 21.8      | 1.04 (0.75, 1.43) |             |
| Total events      | 67          | 66          |             |             |           |             |             |
| Heterogeneity: \(\chi^2 = 8.72, df = 5 (P = 0.12); I^2 = 43\% |             |             |             |             |           |             |             |
| Test for overall effect: Z = 0.22 (P = 0.83) |             |             |             |             |           |             |             |

1.6.2 Gem vs gem + fluoropyrimidine

Berlin et al [43] | 16         | 158         | 16         | 158         | 5.3       | 1.00 (0.52, 1.93) |             |
| Costanzo et al [44] | 3          | 49          | 3          | 41          | 1.1       | 0.84 (0.18, 3.92) |             |
| Cunningham et al [45] | 14        | 247         | 9          | 251         | 3.0       | 1.58 (0.70, 3.58) |             |
| Herrmann et al [46,47] | 10        | 156         | 12         | 159         | 4.0       | 0.85 (0.38, 1.91) |             |
| Scheithauer et al [48] | 0         | 39          | 2          | 40          | 0.8       | 0.20 (0.01, 4.14) |             |
| Subtotal (95%CI) | 649        | 649         |            |             | 14.2      | 1.02 (0.68, 1.53) |             |
| Total events      | 43          | 42          |             |             |           |             |             |
| Heterogeneity: \(\chi^2 = 2.46, df = 4 (P = 0.65); I^2 = 0\% |             |             |             |             |           |             |             |
| Test for overall effect: Z = 0.10 (P = 0.92) |             |             |             |             |           |             |             |

1.6.3 Gem vs gem + camptothecin

Abou-Alfa et al [49] | 12         | 157         | 10         | 168         | 3.2       | 1.28 (0.57, 2.89) |             |
| Kulke et al [50] | 12         | 58          | 5          | 60          | 1.6       | 2.48 (0.93, 6.61) |             |
| Lima et al [51] | 22         | 169         | 28         | 173         | 9.2       | 0.80 (0.48, 1.35) |             |
| Stathopoulos et al [52] | 3         | 70          | 3          | 60          | 1.1       | 0.86 (0.18, 4.09) |             |
| Subtotal (95%CI) | 454        | 461         |            |             | 15.2      | 1.09 (0.75, 1.59) |             |
| Total events      | 49          | 46          |             |             |           |             |             |
| Heterogeneity: \(\chi^2 = 4.30, df = 3 (P = 0.23); I^2 = 30\% |             |             |             |             |           |             |             |
| Test for overall effect: Z = 0.45 (P = 0.65) |             |             |             |             |           |             |             |

1.6.4 Gem vs gem + targeted agent

Cutsem et al [53] | 55         | 342         | 66         | 331         | 22.4      | 0.81 (0.58, 1.12) |             |
| Eckhardt et al [54] | 13        | 118         | 15         | 124         | 4.9       | 0.91 (0.45, 1.83) |             |
| Kindler et al [55] | 21        | 263         | 14         | 277         | 4.5       | 1.58 (0.82, 3.04) |             |
| Kindler et al [56] | 2          | 308         | 0          | 305         | 0.2       | 4.95 (0.24, 102.71) |             |
| Philip et al [57] | 22        | 355         | 35         | 361         | 11.6      | 0.64 (0.38, 1.07) |             |
| Richards et al [58] | 4         | 85          | 11         | 85          | 3.7       | 0.36 (0.12, 1.10) |             |
| Richards et al [59] | 2         | 39          | 3          | 82          | 0.6       | 1.40 (0.24, 8.05) |             |
| Spano et al [60] | 5          | 30          | 5          | 66          | 1.0       | 2.20 (0.69, 7.03) |             |
| Subtotal (95%CI) | 1540       | 1631        |            |             | 48.9      | 0.87 (0.70, 1.08) |             |
| Total events      | 124         | 149         |             |             |           |             |             |
| Heterogeneity: \(\chi^2 = 11.20, df = 7 (P = 0.13); I^2 = 37\% |             |             |             |             |           |             |             |
| Test for overall effect: Z = 1.25 (P = 0.21) |             |             |             |             |           |             |             |
| Total (95%CI) | 3449        | 3552        |             |             | 100.0     | 0.96 (0.82, 1.12) |             |
| Total events      | 283         | 303         |             |             |           |             |             |
| Heterogeneity: \(\chi^2 = 28.20, df = 22 (P = 0.17); I^2 = 22\% |             |             |             |             |           |             |             |
| Test for overall effect: Z = 0.52 (P = 0.60) |             |             |             |             |           |             |             |
| Test for subgroup differences: \(\chi^2 = 1.55, df = 3 (P = 0.67); I^2 = 0\% |             |             |             |             |           |             |             |

Figure 7 Fixed effect model of risk ratio of grade 3 or 4 anemia. CI: Confidence interval.
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| Study or subgroup | Monotherapy | Combination | Risk ratio M-H, fixed, 95%CI | Risk ratio M-H, fixed, 95%CI |
|------------------|-------------|-------------|-----------------------------|-----------------------------|
|                  | Events      | Total       | Total | Weight (%) |                  |                           |
| 1.7.1 Gem vs gem + platinum |             |             |       |            |                  |                           |
| Colucci et al[37] | 1           | 54          | 1     | 53         | 0.7            | 0.98 (0.06, 15.29) |
| Colucci et al[38] | 10          | 189         | 29    | 186        | 4.6            | 0.34 (0.17, 0.68) |
| Helinemann et al[39] | 9           | 85          | 4     | 90         | 2.8            | 2.28 (0.76, 7.45) |
| Kuiken et al[40] | 25          | 58          | 49    | 62         | 6.5            | 0.55 (0.40, 0.75) |
| Louvet et al[41] | 5           | 156         | 22    | 157        | 3.4            | 0.23 (0.09, 0.59) |
| Poplin et al[42] | 35          | 264         | 29    | 263        | 5.8            | 1.20 (0.76, 1.91) |
| Subtotal (95%CI) | 806         | 811         |       | 23.7       | 0.65 (0.36, 1.18) |

Total events 85
Heterogeneity: Tau^2 = 0.35; y^2 = 21.13, df = 5 (P = 0.0008); I^2 = 76%
Test for overall effect: Z = 1.43 (P = 0.15)

1.7.2 Gem vs gem + fluoropyrimidine

| Study or subgroup | Monotherapy | Combination | Risk ratio M-H, fixed, 95%CI | Risk ratio M-H, fixed, 95%CI |
|------------------|-------------|-------------|-----------------------------|-----------------------------|
|                  | Events      | Total       | Total | Weight (%) |                  |                           |
| Berlin et al[43] | 17          | 158         | 30    | 158        | 5.3            | 0.57 (0.33, 0.98) |
| Costanzo et al[44] | 0           | 49          | 1     | 41         | 0.5            | 0.28 (0.01, 6.69) |
| Cunningham et al[45] | 14         | 247         | 28    | 251        | 4.9            | 0.51 (0.27, 0.94) |
| Herrmann et al[46,47] | 12         | 156         | 7     | 159        | 3.6            | 1.75 (0.71, 4.32) |
| Schleithauer et al[48] | 1           | 39          | 0     | 40         | 0.5            | 3.08 (0.13, 73.27) |
| Subtotal (95%CI) | 649         | 649         |       | 14.8       | 0.73 (0.42, 1.28) |

Total events 44
Heterogeneity: Tau^2 = 0.14; y^2 = 6.61, df = 4 (P = 0.16); I^2 = 39%
Test for overall effect: Z = 1.10 (P = 0.27)

1.7.3 Gem vs gem + camptothecin

| Study or subgroup | Monotherapy | Combination | Risk ratio M-H, fixed, 95%CI | Risk ratio M-H, fixed, 95%CI |
|------------------|-------------|-------------|-----------------------------|-----------------------------|
|                  | Events      | Total       | Total | Weight (%) |                  |                           |
| Abou-Alfa et al[49] | 7           | 157         | 26    | 168        | 4.0            | 0.29 (0.13, 0.64) |
| Kulke et al[50] | 25          | 58          | 14    | 60         | 5.3            | 1.85 (1.07, 3.19) |
| Lima et al[51] | 24          | 169         | 34    | 173        | 5.7            | 0.72 (0.45, 1.16) |
| Stathopoulos et al[52] | 0          | 70          | 3     | 60         | 0.6            | 0.12 (0.01, 2.33) |
| Subtotal (95%CI) | 454         | 461         |       | 15.6       | 0.65 (0.26, 1.66) |

Total events 56
Heterogeneity: Tau^2 = 0.63; y^2 = 17.34, df = 3 (P = 0.0006); I^2 = 83%
Test for overall effect: Z = 0.89 (P = 0.37)

1.7.4 Gem vs gem + targeted agent

| Study or subgroup | Monotherapy | Combination | Risk ratio M-H, fixed, 95%CI | Risk ratio M-H, fixed, 95%CI |
|------------------|-------------|-------------|-----------------------------|-----------------------------|
|                  | Events      | Total       | Total | Weight (%) |                  |                           |
| Cutsem et al[53] | 41          | 342         | 50    | 331        | 6.2            | 0.79 (0.54, 1.17) |
| Eckhardt et al[54] | 18         | 118         | 20    | 124        | 5.1            | 0.95 (0.53, 1.70) |
| Kindler et al[55] | 32          | 263         | 33    | 277        | 5.8            | 1.02 (0.65, 1.61) |
| Kindler et al[56] | 1           | 308         | 0     | 305        | 0.5            | 2.97 (0.12, 72.64) |
| Moore et al[57] | 30          | 280         | 28    | 282        | 5.6            | 1.08 (0.66, 1.76) |
| Oettle et al[58] | 17          | 273         | 49    | 273        | 5.4            | 0.35 (0.21, 0.59) |
| Philip et al[59] | 30          | 355         | 24    | 361        | 5.5            | 1.27 (0.76, 2.13) |
| Richards et al[60] | 9           | 85          | 21    | 85         | 4.4            | 0.43 (0.21, 0.88) |
| Richards et al[61] | 10          | 39          | 12    | 82         | 4.3            | 1.75 (0.83, 3.70) |
| Spano et al[62] | 4           | 30          | 13    | 66         | 3.1            | 0.68 (0.24, 1.90) |
| Subtotal (95%CI) | 2093        | 2186        |       | 45.9       | 0.85 (0.62, 1.16) |

Total events 192
Heterogeneity: Tau^2 = 0.14; y^2 = 23.21, df = 9 (P = 0.006); I^2 = 61%
Test for overall effect: Z = 1.05 (P = 0.3)

Total (95%CI) 4002
Heterogeneity: Tau^2 = 0.20; y^2 = 72.14, df = 24 (P < 0.00001); I^2 = 67%
Test for overall effect: Z = 2.23 (P = 0.03)
Test for subgroup differences: y^2 = 0.83, df = 3 (P = 0.84); I^2 = 0%

Figure 8 Random effect model of risk ratio of grade 3 or 4 thrombocytopenia. CI: Confidence interval.

more toxicity than gemcitabine alone. Similar results were found in a previous study[41]. This finding might explain why combination therapy received higher ORR, but without affecting the overall prognosis, as toxicities counterbalanced the positive effects.

In the present analysis, we included several kinds of combination therapies with gemcitabine, which could provide different anti-tumor effects and different uptake and toxicity profiles, including platinum based agents, topoisomerase inhibitors, taxanes, bevacizumab, cetuximab and other biologically targeted agents. However, no significant differences were found between the subgroups, except for side-effects (vomiting). In addition, the analysis of heterogeneity was not significant in most subgroups. This is interesting, and indicates that effectiveness of the different combinations regarding outcomes could not clearly be shown. There are two possible reasons that could explain these results. One is related to gemcitabine uptake receptors. The other one could be the inherent drug-resistant character of pancreatic carcinoma cells and
the effect of the surrounding stroma.

Human equilibrative nucleoside transporter-1 (hENT-1) is the main membrane channel responsible for intracellular bioavailability of gemcitabine. Preclinical and clinical data have revealed that only a minority of patients have high hENT1 expression and reduced levels of hENT-1 expression correlate with increased resistance to gemcitabine[7]. To increase gemcitabine efficiency and
avoid overtreatment, determination of the hENT1 status at the time of diagnosis and modifying gemcitabine to allow it to bypass the receptor may represent a future mode of overcoming gemcitabine resistance[31]. Multidrug resistance proteins, including ABC transporters, have also been implied in drug resistance in pancreatic cancer and limit the efficacy of gemcitabine[40]. The pancreatic stellate cell has a key role in stroma formation and secretes factors that promote pancreatic tumor growth and resistance to radiation and gemcitabine chemotherapy[47]. The hypoxic stroma could be a physical barrier preventing chemotherapeutic drugs from reaching the pancreatic cancer cells per se, and depletion of the stroma could enhance cancer drug delivery[40]. Recently, cancer stem cells and epithelial to mesenchymal transition (EMT)-type cells have been implicated in metastasis formation and drug resistance[46]. Selective targeting of cancer stem cells and EMT-type cells might represent a future strategy to enhance chemosensitivity. The plasma circulating time of gemcitabine is short and its rapid metabolism thus limits tumor uptake. Using novel formulas such as PEGylated gemcitabine may result in a prolonged circulation time, and possibly inducing cytotoxicity at lower concentrations than those required with treatment with the native drug[46]. Pancreatic cancer, including its concurrent stroma, is complex; therefore, treatment with a single anti-tumor agent may not be effective enough. Determining the underlying mechanisms of drug resistance in pancreatic cancer will provide ways of overcoming chemotherapy and provide a foundation for novel therapies.

During the last decade, several meta-analyses have focused on the efficacy of combination therapy in locally advanced or metastatic pancreatic cancer[41,46,47,48]. Most of these studies have reported positive trends or have concluded that combination treatments may improve outcome, but only a limited number of the studies have reported toxicity data, or have only focused on one anti-tumor agent. In the present study, we collected and analyzed the outcomes in different chemotherapeutic subgroups, as well as toxicity, to make the result more comprehensive and convincing. However, several limitations in this analysis should still be considered. Firstly, some endpoints were not evaluated in all of the included randomised controlled trials. Secondly, heterogeneity of certain endpoints in some subgroups might limit the comparability between studies and affect the validity, despite the use of randomized models.

In conclusion, we compared the outcomes of different combination therapies with gemcitabine monotherapy, including ORR, OS, PFS and major toxicity. The results showed that gemcitabine combination therapy leads to a modest improvement in survival, though with more toxicity reported compared with gemcitabine monotherapy.

COMMENTS

Background
Pancreatic cancer is a devastating disease with a dismal prognosis. The major-
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