Original Article

Efficacy and safety of gemcitabine plus capecitabine in the treatment of advanced or metastatic pancreatic cancer: a systematic review and meta-analysis

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Background: Gemcitabine combined the oral fluoropyrimidine capecitabine (GemCap) is an active antitumor therapy in the treatment of advanced or metastatic pancreatic cancer, and has been shown potential synergistic activity in previous clinical trials. In this study, we sought to systematically review and synthesize the efficacy and safety of GemCap in the treatment of advanced or metastatic pancreatic cancer.

Methods: A systematic review was performed through PubMed, Cochrane Library, EMBASE, and Web of Science databases up to Jul 10, 2019 to identify clinical trials that included advanced or metastatic pancreatic cancer patients treated with GemCap. Data of overall survival (OS), progression-free survival (PFS), 1-year survival rate, objective response rate (ORR), disease control rate (DCR) and adverse events were extracted and meta-analyzed.

Results: Fifteen studies were identified for systematic review, of which 13 were included in the meta-analysis. In comparison with Gem monotherapy, the pooled hazard ratios (HR) of GemCap treatment for OS and PFS were 0.85 (95% CI: 0.75–0.95, P=0.007) and 0.80 (95% CI: 0.72–1.04, P=0.0002). The pooled 1-year survival rate, ORR and DCR of GemCap were, respectively, 33.1% (95% CI: 28.7–37.5), 22.9% (95% CI: 17.6–28.3) and 65.7% (95% CI: 56.7–74.8). GemCap combination therapy showed significantly higher ORR (OR: 1.98, 95% CI: 1.34–2.67, P=0.0003) and DCR (OR: 1.41, 95% CI: 1.05–1.88, P=0.02) compared to Gem monotherapy. The most common grade ≥3 hematological toxicities in patients treated with GemCap combination therapy were neutropenia (19.7%), leucocytopenia (7.9%) and anemia (4.9%). The most common grade ≥3 non-hematological toxicities were hand-foot syndrome (6.3%), fatigue (5.7%) and nausea (4.8%).

Conclusions: GemCap combination therapy had an encouraging activity and might be a better treatment strategy compared with Gem alone in the first-line treatment for patients with advanced or metastatic pancreatic cancer.

Keywords: Gemcitabine; capecitabine; combination chemotherapy; pancreatic cancer; meta-analysis

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Introduction

The outcomes of patients with locally advanced or metastatic pancreatic cancer remain poor (1). The median overall survival (OS) for those with stage IV disease is less than 12 months (2,3), even when patients are treated with systemic chemotherapies or combination chemotherapies (4,5).

Since 1997, the single-agent gemcitabine (Gem) has been a standard-of-care first-line treatment for advanced pancreatic cancer, with a significant survival benefit and a safety profile compared to 5-fluorouracil monotherapy (6). Subsequently, various Gem combinations with different chemotherapeutic regimens, comprising paclitaxel, capecitabine (Cap), and platinum, have been applied in advanced pancreatic cancer patients (7,8). MPACT study showed that the combination chemotherapy regimen, Gem/nab-paclitaxel, achieved a higher response rate and longer median overall survival (OS) than Gem (3). Another randomized controlled clinical trial reported that Gem plus oxaliplatin, compared with Gem alone, resulted in an improved objective response rate (ORR) and progression-free survival (PFS) (9). However, in an Eastern Cooperative Oncology Group trial, Gem combined with oxaliplatin failed to improve OS in advanced pancreatic cancer patients (10). Additional combination chemotherapy regimens have also become the treatment strategies for advanced pancreatic cancer. In 2011, a cornerstone study in exploring advanced or metastatic pancreatic cancer chemotherapy was published by Conroy (2). The FOLFIRINOX (a combination of fluorouracil, leucovorin, oxaliplatin, and irinotecan) treatments was associated with a significant improvement in OS versus Gem monotherapy (2). Owing to the greater toxicities, the adoption of FOLFIRINOX for patients with good performance status (11,12). Furthermore, although FOLFIRINOX was associated with slightly longer median OS in relative to Gem-based combination chemotherapy, the difference was not statistically significant (13).

Cap is an oral fluoropyrimidine that has been approved for the treatment of various cancer types (14,15). The improved safety and similar benefit of Cap compared with intravenous fluorouracil and the convenience of oral administration make Cap an attractive treatment option in advance pancreatic cancer (4,16). Cap monotherapy had been demonstrated similar clinical activity compared with single-agent Gem in advanced pancreatic cancer (6,17).

The combination of Gem and Cap (GemCap) has been shown promising antitumor activity in phase I and II clinical trials in patients with advanced pancreatic cancer (18-21). Although GemCap was associated with a trend toward improved OS but failed to improve OS at a statistically significant level compared with Gem alone (4,16,22). At the moment, both GemCap combination therapy and Gem monotherapy are the general treatment strategies for advanced or metastatic pancreatic cancer in our hospital. We have noticed that GemCap combination therapy might be superior to Gem monotherapy, however, published clinical data remain controversial and could not directly support this hypothesis. Therefore, associated clinical trials published up to 2019 were collected to assess the benefit and risk of GemCap combination chemotherapy in patients with advanced or metastatic pancreatic cancer. Here, we systematically reviewed the reported clinical trials and performed a meta-analysis of the available data regarding GemCap therapy on survival estimates, tumor response rates, and tolerability. We conducted the meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline (available at http://dx.doi.org/10.21037/apm-20-45) (23).

Methods

Search strategy

A systematic literature search was performed in the electronic databases PubMed, Cochrane Library, Web of Science, and EMBASE. The last search was run on Jul 10, 2019. Search terms included: "advanced pancreatic cancer or advanced pancreatic adenocarcinoma or metastatic pancreatic cancer or metastatic pancreatic adenocarcinoma", "gemcitabine", "capecitabine", and "trial or clinical trial or randomized clinical trial or randomized controlled trial". Only articles written in English were assessed. The references of articles were searched for more eligible studies.

Selection criteria

Eligible studies included advanced or metastatic pancreatic cancer patients of any age who received GemCap, regardless of subsequent surgical therapy or radiotherapy. Patients treated with GemCap plus other chemotherapy or target therapy at the same time were excluded. Conference abstracts without full text and retrospective studies were either excluded. For multiple published articles that were identified reporting on the same clinical trial, the one with the most complete publication data was eligible. Any discrepancies were resolved by discussion.

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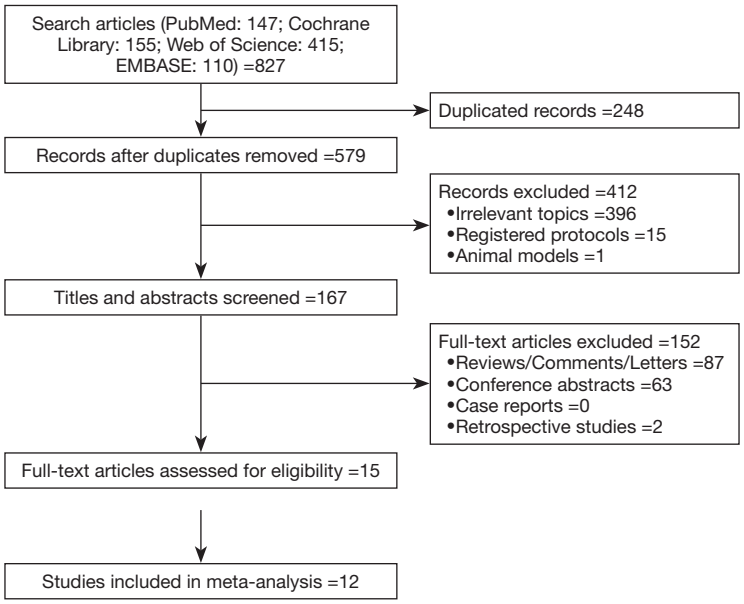

Figure 1 Flow chart of the relevant studies selection process.

Data extraction and quality assessment

The primary outcome was OS, and the second outcomes included PFS, 1-year survival rate, ORR, DCR, and adverse events. Two authors (BW and BX) independently extracted information from the full texts and supplementary materials. Any discrepancies were resolved by discussion. The following study details were collected from each eligible study: first author, year of publication, study design, number of patients, line of therapy, OS, PFS, 1-year survival rate, ORR, DCR, and adverse events. The methodological quality of each eligible study was evaluated by two authors (BW and BX) according to the Jadad scale (24-26).

Statistical analysis

Survival outcomes from randomized controlled trials were assessed by HR (OS and PFS)/OR (ORR and DCR) and 95% CIs using RevMan version 5.3 software (Cochrane Collaboration's Information Management System). We tested for heterogeneity used I^2. When $P \geq 0.10$ and $I^2 \leq 50\%$, the heterogeneity test showed no statistical significance. Thus, a fixed-effects model was used. Otherwise, a random-effects model was applied. $P<0.05$ was considered statistically significant.

Pooled incidences of 1-year survival rate, ORR, DCR, and adverse events were done using STATA statistical software (version 14.0). The analyses were conducted in a Random-effects model. Potential publication bias was examined using Egger's test (27-29).

Results

Study selection

The initial search identified 827 relevant publications, of which 248 were duplicates; an additional 564 were excluded based on eligibility criteria, leaving 15 studies (4,16,18,19,21,22,30-38) for further analysis (*Figure 1*).

Study characteristics

Study characteristics are presented in *Table 1*. Nine studies were multi-center clinical studies, two were single-center clinical studies, and the other three did not mention it. One study was a phase I study, one was a phase I/II study, eight were phase II studies, and the other five were randomized controlled phase III trials. Patients in 13 studies received first-line GemCap chemotherapy and in two studies were given second- or more-line GemCap chemotherapy. Using the Jadad score, nine studies were classified as low quality (a score of ≤2), whereas six studies as high quality (a score of ≥3).

Effectiveness outcomes

All studies reported an OS (*Table 2*). Three studies were

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Table 1 Characteristic of the eligible studies in the analysis

Study	Year	Single-/ Multi-center	Phase	Line of therapy	No. Patients	Age (years)	Chemotherapy	NCI-CTC	Jadad score
Hess	2003	Multi-	I/II	First	36	68 [46–79]	Gem: 1,000 mg/m^2, day 1, 8; Cap: 500/650/800 mg/m^2, twice daily, day 1–14; every 3 weeks	NR	1
Scheithauer	2003	Multi-	II	First	41	64 [40–75]	Gem: 2,200 mg/m^2, day 1; Cap: 1,250 mg/m^2, twice daily, day 1–7; every 2 weeks	NR	3
Stathopoulos	2004	Multi-	II	First	53	65 [42–78]	Gem: 1,000 mg/m^2, day 1, 8; Cap: 650 mg/m^2, twice daily, day 1–14; every 3 weeks	NR	1
Herrmann	2007	Multi-	III	First	160	NR	Gem: 1,000 mg/m^2, day 1, 8; Cap: 650 mg/m^2, twice daily, day 1–14; every 3 weeks	2.0	3
Park	2007	Single-	II	First	45	55 [33–76]	Gem: 1,000 mg/m^2, day 1, 8, 15; Cap: 830 mg/m^2, twice daily, day 1–21; every 4 weeks	3.0	1
Song	2008	Multi-	II	First	63	59 [38–75]	Gem: 1,000 mg/m^2, day 1, 8; Cap: 1,000 mg/m^2, twice daily, day 1–14; every 3 weeks	2.0	1
Boeck	2008	Multi-	II	Second+	64	64 [47–75]	Gem: 1,000 mg/m^2, day 1, 8; Cap: 825 mg/m^2, twice daily, day 1–14; every 3 weeks	2.0	2
Cunningham	2009	Multi-	III	First	267	62 [37–82]	Gem: 1,000 mg/m^2, day 1, 8, 15; Cap: 830 mg/m^2, twice daily, day 1–21; every 4 weeks	2.0	3
Michael	2009	NR	I	First	20	64 [41–80]	Gem: 20–50 mg/m^2, day 1, twice per week; Cap: 800–2,000 mg/m^2, twice daily, day 1–5; each week	2.0	1
Choi	2012	Single-	II	First	50	53 [39–76]	Gem: 1,000 mg/m^2, day 1, 8, 15; Cap: 830 mg/m^2, twice daily, day 1–21; every 4 weeks	3.0	1
Lee	2012	NR	II	First+	43	61 [42–76]	Gem: 1,250 mg/m^2, day 1, 8; Cap: 950 mg/m^2, twice daily, day 1–14; every 3 weeks	3.0	1
Middleton	2014	Multi-	III	First	358	62 [55–69]	Gem: 1,000 mg/m^2, day 1, 8, 15; Cap: 830 mg/m^2, twice daily, day 1–21; every 4 weeks	3.0	3
Lee	2017	Multi-	III	First	108	64 [37–80]	Gem: 1,000 mg/m^2, day 1, 8, 15; Cap: 830 mg/m^2, twice daily, day 1–21; every 4 weeks	4.0	3
Neoptolemos	2017	Multi-	III	First	364	65 [37–81]	Gem: 1,000 mg/m^2, day 1, 8; Cap: 830 mg/m^2, twice daily, day 1–14; every 3 weeks	4.0	3
Quan	2017	NR	II	First	16	71 [50–81]	Gem: 1,000 mg/m^2, day 1, 8; Cap: 650 mg/m^2, twice daily, day 1–14; every 3 weeks	CTCAE 4.0	1

Gem, gemcitabine; Cap, capecitabine; NCI-CTC, National Cancer Institute common toxicity criteria; CTCAE, Common Terminology Criteria for Adverse Events; NR, not reported.

excluded from survival analyses because these patients underwent a resection after GemCap (35,37,38), which might potentially improve survival. Patients in two studies had been treated with radiotherapy (33,38). Two studies did not report 1-year survival rates (22,33). The median OS ranged from 6.4 to 11.2 months across studies. When patients underwent pancreaticoduodenectomy, the median OS ranged from 14.3 to 28.0 months. Data regarding OS from three studies were collected (4,16,22), including 534 patients in the GemCap group and 532 patients in the Gem group. Forest plots showed that GemCap had a 15% lower risk of death compared to Gem (HR: 0.85, 95% CI: 0.75–0.95, P=0.007) (*Figure 2*). OS at 1 year was 32.0% (95% CI: 28.1–35.9) (*Figure 3*). Publication bias was not observed in the result of Egger's test (P=0.185 >0.05). The median PFS ranged from 3.9 to 6.5 months, much lower than that of patients who received pancreaticoduodenectomy (10 months). PFS data extracted from three studies were

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Table 2 Survival outcomes of the patients in the selected studies

Study	Median OS, mo	Median TTP, mo	1-year survival rate
Hess 2003	6.4 (95% CI: 4.9–7.8)	NR	33.0%
Scheithauer 2003	9.5 (range: 1.0–23.0+)	5.1 (range: 1.0–13.5)	31.8%
Stathopoulos 2004	8.0 (range: 1.0–15.5)	6.5 (range: 3.5–15.5)	34.8%
Herrmann 2007	8.4 (95% CI: 6.3–9.8)	4.3 (95% CI: 6.3–9.8)	32.0%
Park 2007	10.4 (95% CI: 6.2–14.5)	5.4 (95% CI: 1.8–9.0)	39.3%
Song 2008	7.5 (95% CI: 5.0–10.0)	3.9 (95% CI: 3.5–5.7)	27.1%
Boeck 2008	9.0 (95% CI: 7.7–11.5)	5.7 (95% CI: 3.6–6.3)	33.0%
Cunningham 2009	7.1 (95% CI: 6.2–7.8)	5.3 (95% CI: 4.5–5.7)	24.3%
Michael 2009	11.2 (95% CI: 9.4–14.4)	NR	NR
Choi 2012	10.0 (95% CI: 5.7–16.7)	6.5 (95% CI: 2.3–8.7)	45.0%
Lee 2012	16.6 (95% CI: 12.1–20.2)	10.0 (95% CI: 8.0–12.0)	70.0%
Middleton 2014	7.9 (95% CI: 7.1–8.8)	6.4 (95% CI: 4.8–7.1)	33.7%
Lee 2017	10.3 (95% CI: 7.9–12.7)	6.2 (95% CI: 5.1–7.3)	NR
Neoptolemos 2017	28.0 (95% CI: 23.5–31.5)	NR	84.1%
Quan 2017	14.3 (95% CI: 10.8–16.9)	NR	60.0%

OS, overall survival; TTP, time to progression; NR, not reported.

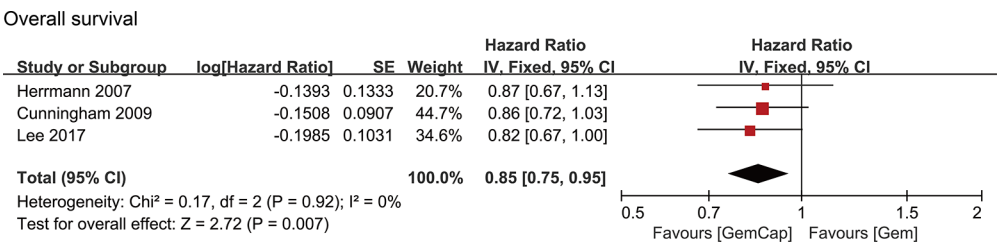

Figure 2 Forest plot of hazard ratios for overall survival in patients between GemCap group and Gem group. GemCap: gemcitabine plus capecitabine; GEM, gemcitabine alone; SE, standard error; IV, inverse variance statistical method; CI, confidence interval; I2, index of heterogeneity; Fix, fixed effect analysis model.

meta-analyzed (4,16,22). Compared with Gem alone, GemCap showed a 20% lower risk of disease progression (HR: 0.80, 95% CI: 0.72–0.90, P=0.0002) (*Figure 4*).

Rate estimates of objective response (complete response and partial response) and disease control (complete response, partial response, and stable disease) were highly heterogeneous (respectively, P<0.001 and I^2 =79.4%; P<0.001 and I^2 =84.4%). For the whole study cohort, the estimated fraction of patients with objective response was 22.9% (95% CI: 17.6–28.3%) (*Figure 5*); disease control was averaged to 65.7% (95% CI: 56.7–74.8%) (*Figure 6*). Egger's test did not show evidence of publication bias (ORR: P=0.058 >0.05; DCR: P=0.226 >0.05). In three phase III trials, in comparison with Gem, the pooled relative risk for complete response and partial response was significantly higher after combination therapy (OR: 1.98, 95% CI: 1.34–2.67, P=0.0003) (*Figure 7A*). Two phase III trials were identified reporting disease control. GemCap showed significantly higher DCR compared to Gem alone (OR: 1.41, 95% CI: 1.05–1.88, P=0.02) (*Figure 7B*).

Toxicity

In 11 studies, the adverse events were reported using the

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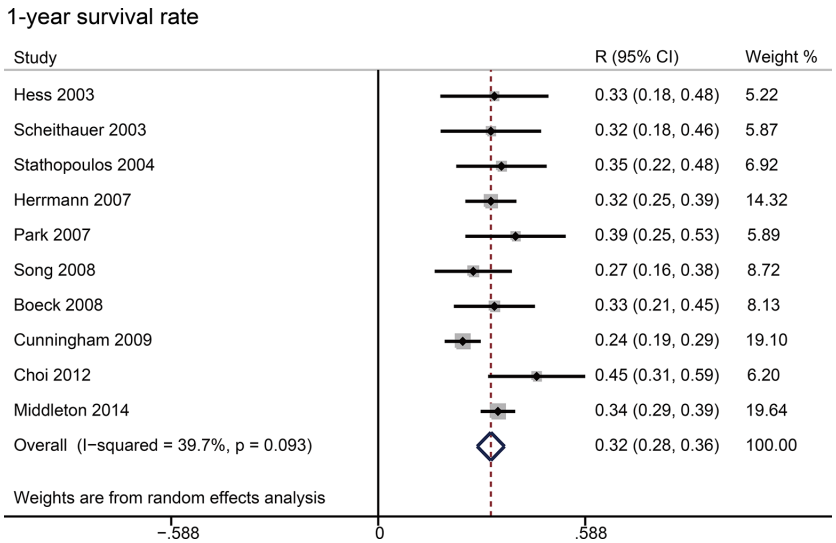

Figure 3 Forest plot of the 1-year survival rates in patients treated with GemCap. R, rate.

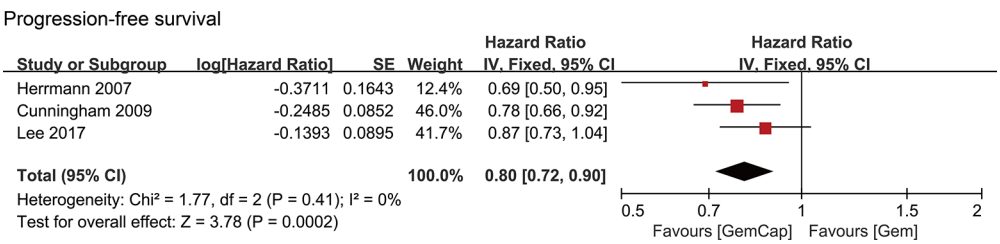

Figure 4 Forest plot of hazard ratios for progression-free survival in patients between GemCap group and Gem group.

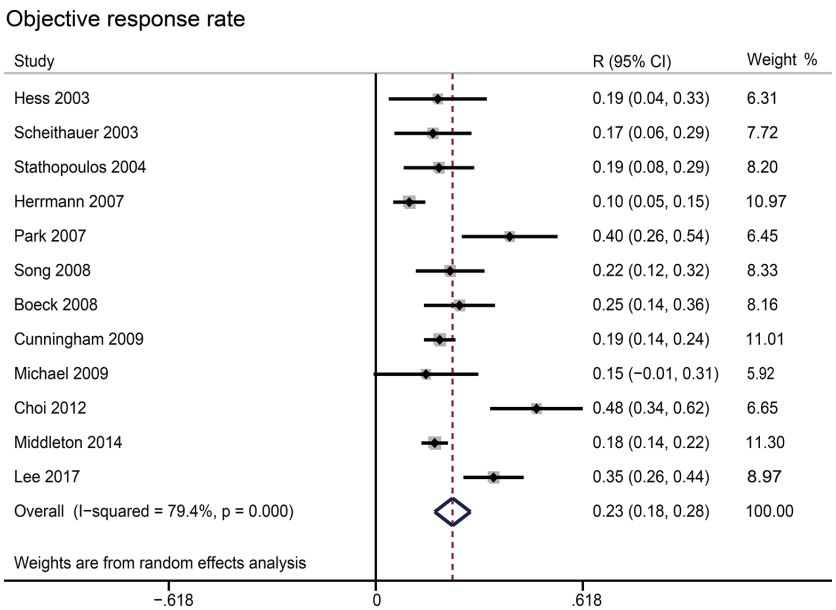

Figure 5 Forest plot of the objective response rates in patients treated with GemCap.

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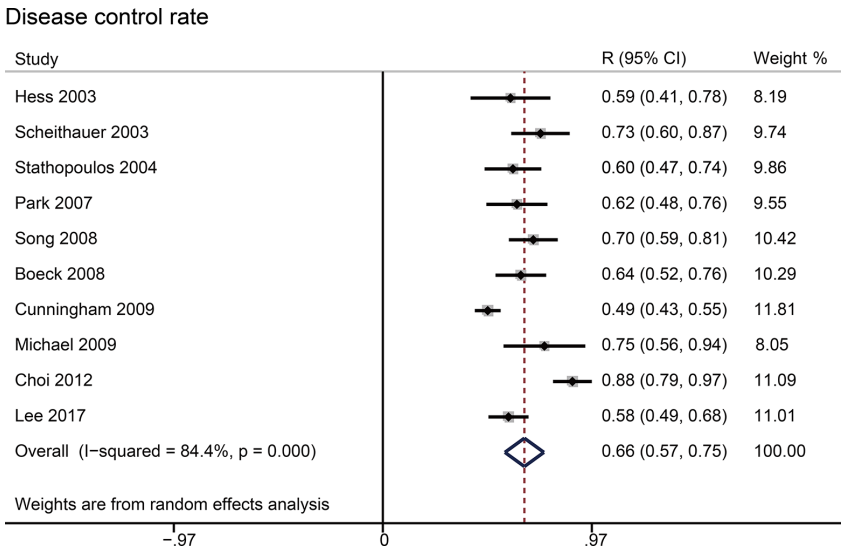

Figure 6 Forest plot of the disease control rates in patients treated with GemCap.

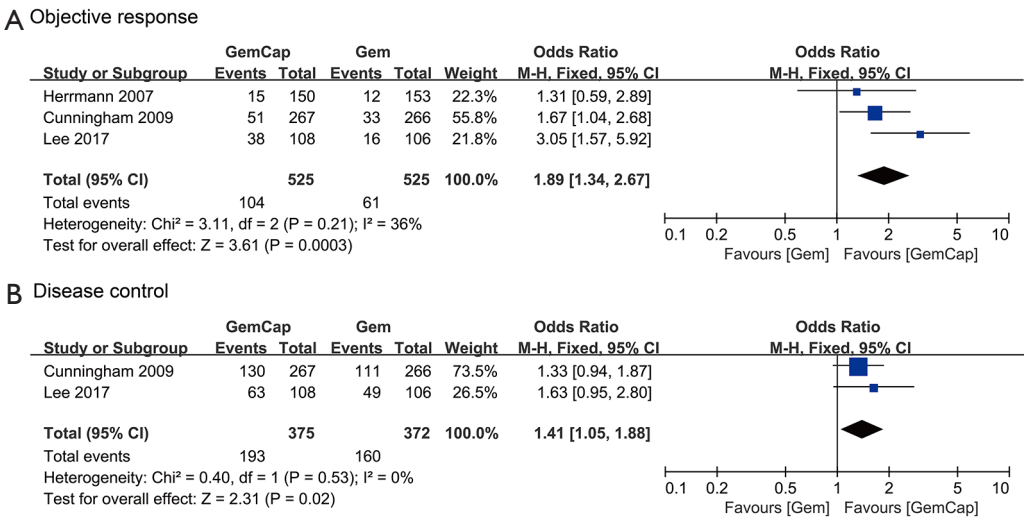

Figure 7 Forest plot of odds ratios for objective response (A) and disease control (B) in patients between GemCap group and Gem group.

National Cancer Institute common toxicity criteria (NCI-CTC) (version 2.0 =5; version 3.0 =4; version 4.0 =2). And only in one study, toxicities was reported using the Common Terminology Criteria for Adverse Events (CTCAE, 4.0). Three studies did not clearly describe the evaluation criteria that they used (18,19,21). One death was reported by Stathopoulos in 2004 (21). The cause of death was upper gastrointestinal bleeding due to anticoagulant therapy of a deep venous thrombosis. One patient dead was reported by Herrmann in 2007 owing to several grade 4 adverse events (diarrhea, intrahepatic cholestasis, hyperbilirubinemia, and febrile infection) (16). There were four deaths reported by Middleton in 2014 (36) and four by Neoptolemos in 2017 (37) because of drug-related toxic effects. The pooled incidences of any-grade hematological adverse events were 41.9% (95% CI: 20.7–63.1%) for anemia, 65.6% (95% CI: 56.4–74.8%) for leucocytopenia, 42.2% (95% CI: 28.0–56.4%) for neutropenia, and 31.7% (95% CI: 21.6–41.7%) for thrombocytopenia. The pooled incidences of any-grade non-hematological adverse events were 25.2% (95% CI: 19.6–30.9%) for hand-foot syndrome, 41.3% (95% CI: 20.9–61.7%) for nausea, 33.4% (95% CI: 29.2–37.6%) for

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Table 3 Pooled analysis of any-grade adverse events.

Toxicities	Incidence	95% CI
Hematological		
Anemia	41.9%	20.7–63.1%
Leucocytopenia	65.6%	56.4–74.8%
Neutropenia	42.2%	28.0–56.4%
Thrombocytopenia	31.7%	21.6–41.7%
Non-hematological		
Hand-foot syndrome	25.2%	19.6–30.9%
Nausea	41.3%	20.9–61.7%
Vomiting	33.4%	29.2–37.6%
Fatigue	38.2%	5.7–70.7%
Diarrhea	34.8%	30.8–38.7%
Mucositis	16.2%	12.7–19.6%
Constipation	27.6%	14.5–40.7%
Alopecia	24.1%	6.5–41.7%

CI, confidence interval.

Table 4 Pooled analysis of grade ≥3 adverse events.

Toxicities	Incidence	95% CI
Hematological		
Anemia	4.9%	3.1–6.6%
Leucocytopenia	7.9%	3.1–12.6%
Neutropenia	19.7%	12.8–26.7%
Febrile neutropenia	1.2%	0–2.4%
Thrombocytopenia	4.7%	2.3–7.0%
Non-hematological		
Hand-foot syndrome	6.3%	2.8–9.8%
Nausea	4.8%	3.5–6.2%
Vomiting	4.6%	3.3–6.0%
Fatigue	5.7%	0.1–11.3%
Diarrhea	3.6%	2.5–4.7%
Mucositis	2.0%	0.7–3.3%
Stomatitis	2.7%	1.1–4.3%
Constipation	2.8%	0.5–5.1%

CI, confidence interval.

vomiting, 38.2% (95% CI: 5.7–70.7%) for fatigue, 34.8% (95% CI: 30.8–38.7%) for diarrhea, 16.2% (95% CI: 12.7–19.6%) for mucositis, 27.6% (95% CI: 14.5–40.7%) for constipation, and 24.1% (95% CI: 6.5–41.7%) for alopecia (*Table 3*). The pooled incidences of grade ≥3 hematological adverse events were 4.9% (95% CI: 3.1–6.6%) for anemia, 7.9% (95% CI: 3.1–12.6%) for leucocytopenia, 19.7% (95% CI: 12.8–26.7%) for neutropenia, 1.2% (95% CI: 0–2.4%), and 4.7% (95% CI: 2.3–7.0%) for thrombocytopenia. The pooled incidences of grade ≥3 non-hematological adverse events were 6.3% (95% CI: 2.8–9.8%) for hand-foot syndrome, 4.8% (95% CI: 3.5–6.2%) for nausea, 4.6% (95% CI: 3.3–6.0%) for vomiting, 5.7% (95% CI: 0.1–11.3%) for fatigue, 3.6% (95% CI: 2.5–4.7%) for diarrhea, 2.0% (95% CI: 0.7–3.3%) for mucositis, 2.7% (95% CI: 1.1–4.3%) for stomatitis, and 2.8% (95% CI: 0.5–5.1%) for constipation (*Table 4*).

Discussion

In our study, the addition of Cap to Gem showed a significant improved OS (P=0.007) and PFS (P=0.0002) with no significant intertribal heterogeneity (I^2 =0%, P>0.05) compared with Gem alone. After GemCap therapy, 22.9% (95% CI: 17.6–28.3%) of patients achieved objective response and 65.7% (95% CI: 56.7–74.8%) of patients achieved disease control. About ten deaths were attributed to GemCap. A potential mechanism in explaining the results is that a Cap-induced decrease in cytidine deaminase activity could lead to the improvement of survival outcomes with GemCap therapy, but also interpret the toxicities associated with the combination treatment (39).

Previously, in a retrospective study (40), the OS was significantly improved with GemCap (12.1 months) compared to Gem (10.4 months) (HR: 0.52, 95% CI: 0.28–0.96, P=0.037). Moreover, GemCap significantly reduced the hazard of disease progression compared with Gem monotherapy (HR: 0.46, 95% CI: 0.27–0.79, P=0.035). The overall ORR of GemCap in Lim's study was 21.2%, which was much higher than that of Gem (12.7%). Neutropenia was the most common grade ≥3 hematologic toxicity, but none of the patients had grade ≥3 hand-foot syndrome in this study. Another retrospective study reported that median OS was 8.7 months (95% CI: 6.7–10.7 months), 1-year survival rate after commencing GemCap was 34% (95% CI: 25–43%), and incidence of grade ≥3 hand-foot syndrome was approximately 8% (41). Notably, both trials above suggested GemCap as a more effective regimen than Gem

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monotherapy in the advanced or metastatic setting.

Adding capecitabine to standard gemcitabine reduced the hazard of death. Accordingly, phase I/II studies were conducted to determine the safety and efficacy of a first-line regimen combining Gem, Cap and oxaliplatin. Petrioli reported an ORR of 35.2% and a DCR of 79.4% in the treatment of combining all three drugs in advanced pancreatic cancer (42). Hess showed ORR in 41% of patients and DCR in 78% of patients (43). However, hematologic and non-hematologic toxicities were more severe with a combination of three-agent therapy in both studies.

The safety profile of gemcitabine and fluoropyrimidine is known to be non-overlapping, and combination therapy of these drugs is well tolerated. Furthermore, both drugs target the pyrimidine biosynthesis pathway and may, therefore, exert synergistically (44,45). Another oral fluoropyrimidine, S-1, consists of tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate at a molar ratio in 1:0.4:1, and inhibits dihydropyrimidine dehydrogenase. S-1 had proven efficacy in metastatic pancreatic cancer (46). An early phase II study of S-1 for metastatic pancreatic cancer reported a 21.1% partial response rate (47). Furthermore, two phase II studies of combined gemcitabine and S-1 in patients with advanced pancreatic cancer suggested that repeated 3-week cycles of combination chemotherapy with gemcitabine and S-1 were effective, convenient, and safe (48,49). A recent meta-analysis of the addition of S-1 to Gem-based chemotherapy showed a statistically significant improvement in survival and suggested Gem plus S-1 as first-line chemotherapy for patients with advanced or metastatic pancreatic cancer (50).

Gem in combination with target agents is a new therapeutic modality. A meta-analysis reported that the ORR was 14.4% (95% CI: 11.6–17.7%), DCR was 55.0% (95% CI: 51.5–58.5%), and 1-year survival rate was 28.5% (95% CI: 24.0–33.4%) in patients treated with Gem plus erlotinib (51). These data suggested that Gem combined with target agents could be a first-line therapeutic option for advance or metastatic pancreatic cancer.

For patients with local advanced and inoperable pancreatic cancer, the potential for tumor down-staging with induction chemo-/radio-therapy is alluring to maximize the chance of complete resection. The results from Andriull *et al.* supported the claim: among 362 unresectable patients evaluated in 13 trials, 28% (95% CI: 21–35%) of patients were down-staged sufficiently to an objective response. However, the relatively low resection rate after preoperative therapy in this population of patients required very candid discussions with patients regarding the goal of therapy. Fortunately, 72% (95% CI: 59–86%) of surgically explored patients underwent a successful pancreatic resection (52).

Treatment tolerability is strictly correlated with quality of life. GemCap was associated with worse hematologic and non-hematologic toxicities than Gem. Nonetheless, there was an improvement in the quality of life during treatment with the combination therapy regimen, suggesting the primary aim of an effective treatment in delaying the quality-of-life deterioration. In line with our findings, the GemCap plus oxaliplatin, despite the high incidence of treatment related toxicities, was able to increase the time to definitive deterioration of quality of life (42,43). Bernhard *et al.* prospectively compared the quality of life in patients receiving GemCap versus Gem. In this phase III trial, in advanced pancreatic cancer, no difference in the quality of life was found between single-agent Gem and combination therapy (53). These studies indicated that an effective combination of chemotherapy could help maintain a good quality of life in patients with advanced pancreatic cancer.

Limitations

There were several limitations in the present study. First, there were only three randomized controlled trials included in the meta-analysis. Although no publication bias was shown in the single-arm analyses, heterogeneity across the trials might bias the results. Second, the dosages of GemCap were inconsistent and additional therapies (e.g., radiotherapy) had been added to the chemotherapy. Third, pooled analyses of Gem or Cap monotherapy were not comprised in this study as we mainly focused on the combination therapy. Future studies are needed to comprehensively compare the efficacy of gemcitabine plus capecitabine combination therapy, gemcitabine monotherapy, and capecitabine monotherapy.

In conclusion, this meta-analysis of advanced or metastatic pancreatic cancer patients treated with GemCap showed a favorable median OS, median PFS, 1-year survival rate, ORR, and DCR. The present study provided additional evidence for selecting GemCap as a superior chemotherapy regimen to Gem alone in the first-line treatment for advanced or metastatic pancreatic cancer.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-45). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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