RESEARCH ARTICLE

An Updated Meta-analysis and System Review:is Gemcitabine+Fluoropyrimidine in Combination a Better Therapy Versus Gemcitabine Alone for Advanced and Unresectable Pancreatic Cancer?

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Abstract

Background: Pancreatic cancer ranks fourth in deaths caused by cancers throughout the world. Gemcitabine chemotherapy is the primary method of treatment of advanced pancreatic cancer, and in asco2014, it is still first-line chemotherapy. Howeve,r gemcitabine+fluorouracil regimens are also licensed and widely used worldwide. Clinical trials are the best way to evaluate drug efficacy. In this study, we performed a systematic review and a meta-analysis of randomized controlled trials (RCTs) to assess whether gemcitabine+fluoropyrimidine combination therapy improves the prognosis of unresectable pancreatic cancer compared with gemcitabine treatment alone. Materials and Methods: A quantitative up-to-date meta-analysis was undertaken to investigate the efficacy of gemcitabine-based combination treatment compared with gemcitabine monotherapy for locally advanced or metastatic pancreatic cancer. Inclusion was limited to high-quality randomized clinical trials. Results: A total of 12 studies were included in the present analysis, with a total of 3,038 patients recruited. The studies were divided into three subgroups including 5-FU / CAP / S-1 combined with gemcitabine. For the primary endpoint of overall survival (OS), gemcitabine-based combination therapy demonstrated significantly better outcome (HR, 0.88; 95% CI, 0.81-0.95) than gemcitabine monotherapy. The analysis of progression free survival (PFS) also provided a significant result for the combined therapy in a total of 8 trials (2,130 patients) (HR, 0.74; 95% CI, 0.63-0.86). With subgroup analysis according to the method of dosing delivery, we found that in the injection group with 3 trials (889 patients), a negative result was found (HR, 0.93; 95% CI, 0.77-1.12); while a positive result was observed in the oral group with 9 trials (2,149 patients) (HR, 0.87; 95% CI, 0.80-0.95). Conclusions: Gemcitabine combination therapy provides a modest improvement of survival, but is associated with more toxicity compared with gemcitabine monotherapy.

Keywords: Gemcitabine - fluorouracil - S-1 - capecitabine -meta-analysis - pancreatic cancer

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Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the US and it remains a highly lethal malignancy despite advances in treatment (el-Kamar et al., 2003; Bond-Smith et al., 2012). In 2009 there were 42,470 new cases of pancreatic cancer and 35, 240 deaths from the disease (Bayoglu et al., 2014). At initial diagnosis, 50% of patients present with metastatic disease, 30% present with a locally advanced tumor, and only 20% are resectable. Surgical resection remains the only potentially curative therapy. The large number of recurrences and/or distant failures following resection suggest that microscopic metastases continue to bean obstacle to better outcomes. Patterns of spread included direct extension, lymphatic spread to regional lymph nodes, and hematogenous spread to distant sites. For all stages, the 1- and 5-year survival rates are 25% and 6%, respectively. Even for patients diagnosed with localized disease, the 5-year survival rate is only 22% (Jemal et al., 2008). Gemcitabine has represented the reference standard for the treatment of advanced pancreatic cancer (APC) since 1996, based on improvements in overall survival (OS) and clinical benefit response (Burris et al., 1997). However, therapeutic options for this disease are rapidly evolving, with 2 recently reported phaseIII studies indicating the superiority of multidrug regimens over gemcitabine monotherapy. Fluorouracil is the traditional chemotherapy drug in the treatment of gastrointestinal cancer. S-1 is a new oral fluoropyrimidine derivative in which tegafur is combined with 2 5-chloro-2, 4-dihydroxy pyridine modulators and oteracil potassium, a potentiator of5-fluorouracil's (5-FU's) antitumor activity that also decreases gastrointestinal toxicity. In Japan, clinical

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trials ofS-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) have been conducted since the early 2000s for patients with pancreatic cancer. Combination chemotherapy with gemcitabine and S-1 is reportedly well tolerated and active against advanced pancreatic cancer (Ueno et al., 2005; Nakamura et al., 2006; Kim et al., 2009; Lee et al., 2009; Oh et al., 2010; Tong et al., 2014). To investigate whether gemcitabine combined with fluoropyrimidines could lead to better therapeutic effect without more serious side effects of chemotherapy, a lot of stage II, III random clinical trials have already been undertaken. As far as we know, though some articles investigated this topic, however, there is lacking of a comprehensive and accurate summary on these issues for over five years, Therefore we conducted this systematic review ofthe published RCTs to obtain a full view of the efficacy and safety profile of Gemcitabine+Fluoropyrimidines for treating pancreatic cancer compared with Gemcitabine alone. This meta-analysis provides helpful insight in understanding the efficacy of therapeutics in the treatment of advanced pancreatic cancer.

Materials and Methods

Search strategy

We collected the eligible trials by searching the Cochrane Central Register of Controlled Trials (CENTRAL), PUBMED, EMBASEand WEB OF SCIENCE up to Nov. 2014. The search was limited topublished studies of humans by using the following search keywords and Medical Subject Headings terms: (((((((((((neoplasm) OR neoplasms) OR cancer) OR cancers) OR adenoma) OR adenomas) OR carcinoma) OR carcinomas)) AND ((Pancreatic) OR Pancreas)) AND ((Gemcitabine) OR Gemzar))) AND (((s-1) OR ((Capecitabine) OR Xeloda)) OR (((Fluorouracil) OR 5-FU) OR FU)). We alsoscrutinized the reference citations in the retrieved articles so asnot to miss any additional eligible studies.

Inclusion criteria

All relevant RTCs were considered. Abstracts or unpublisheddata were included if sufficient information on study design, characteristics of participants, interventions and outcomes wereavailable and if the full information and final results wereconfirmed by the first author.

Exclusion criteria

We excluded quasi-randomized studies that were considered the most insufficient quality. Cross-over studies were excluded inorder to assess the overall treatment effect on survival.

Data extraction

Two reviewers (C. Tu and F. Zheng) independentlyextracted the data from all the included studies. Any differencesin data extraction were resolved by consensus with participation of a third reviewer analyzing the data of the original articles. When the relevant data was not found in the published article, we contacted the primary author to gain the original data. Theprimary outcome of this analysis was OS, while the secondaryoutcomes included progression free survival (PFS) or ORR. We used the methods of summarizing hazard ratios (HRs) of time-to-event data (OS and PFS). The HRs of time-to-event data (OSand PFS) were extracted from the original studies or accountedfrom the reported number of events and the corresponding value of the log-rank statistics, or by reading off survival curves. We used the name of the first author and the year of publicationof the article for identification.

Statistical analysis

The pooled HR and its corresponding 95% CI were calculated to assess the outcome of the therapy. Heterogeneity among studies was assessed by Q-test and the I^2 statistic. I^2 describes percentage of total variation due to between-study heterogeneity rather than chance. In the outcome of substantial heterogeneity (I^2>50%), pooled HR was calculated by random effects model (REM); when the inverse variance (I^2<50%) came out, fixed effects model (FEM) was applied. Subjects were grouped by different combined cytotoxic agents and the types of dosing delivery ways to observe the possible factors affecting curative effect. In each analysis, an influence analysis was performed to validate the stability of outcomes by sequential omitting of each individual study. A study was suspected to excessively influence the final point estimation if its omitted analysis lied beyond the 95% CI of the combined analysis. Publication bias was estimated by funnel plot and Egger linear regression test .

All statistical analyses were performed with the software StataSE12. 0. All tests of our analysis were 2-sided and P<0.05 was considered statistically significant.

Results

Study selection

Figure 1 illustrates the process of study selection. 145 Potentially relevant studies were included from search of COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS, PUBMED, EMBASE and WEB OF SCIENCE, 7 Studies identified were selected by hand search of references, after exclusion on basis of title and abstract which were unrelated to our study design, we chose to read 31 full text of articles, and finally identified 12 studies in our meta-analysis.

Trials comparing single-agent gemcitabine with gemcitabine combined with other cytotoxic agents

This analysis evaluated 12 trials (3,038 patients) comparing single-agent gemcitabine with gemcitabine-based combinations with other cytotoxic agents. For the primary endpoint of OS, the gemcitabine-based combination therapy was observed significantly better outcome (FEM: pooled HR, 0.88; 95% CI, 0.81-0.95; p=0.001) than gemcitabine in monotherapy (Figure 2). There was no with no significant heterogeneity (I^2=0.0%, p=0.466).

In subgroup analysis, there was no significantly better outcome in Group Gem *vs*. Gem + 5-FU (FEM: pooled HR, 0.93; 95% CI, 0.77-1.12; p=0.451; I^2=40.8%,

p=0.185) in 3 trials (889 patients); and the significant results were found in Group Gem *vs*. Gem + Cap with 5 trials (1273 patients) (FEM: pooled HR, 0.89; 95% CI, 0.80-0.99; p=0.038; I^2=0.0%, p=0.469) and Group Gem *vs*. Gem +S-1 with 4 trials (876 patients) (FEM: pooled HR, 0.83; 95% CI, 0.72-0.96; p=0.011; I^2=0.0%, p=0.466).

The analysis of PFS also provided a significant result for the combined therapy in total 8 trials (2,130 patients) (REM: pooled HR=0.74; 95% CI, 0.63-0.86; p<0.001; I^2=54. 5%, p=0.032) (Figure 3). An advantage result for therapy Gem + Cap (4 trials including 1, 254 patients) was observed in subgroup analysis (FEM: pooled HR, 0.64; 95% CI, 1.31-1.91; p<0.001; I^2=0.0%, p=0.921), but the result was negative in Group Gem *vs*. Gem + S-1 with 4 trials (876 patients) (REM: pooled HR=0.85; 95% CI, 0.67-1. 08; p<0.076; I^2=65.4%, p=0.034).

Trials comparing single-agent gemcitabine with gemcitabine combined therapy in different dosing delivery ways

When we conducted subgroup analysis according to the dosing delivery ways, we found different results in the two groups. In the injection group with 3 trials (889 patients), a negative result was found (FEM: pooled HR, 0.93; 95% CI, 0.77-1.12; p=0.451; I^2=40.8%, p=0.185); while a positive result was observed in the oral group with 9 trials (2,149 patients) (FEM: pooled HR, 0.87; 95% CI, 0.80-0.95; p=0.001; I^2=0.0%, p=0.540), showed in Figure4.

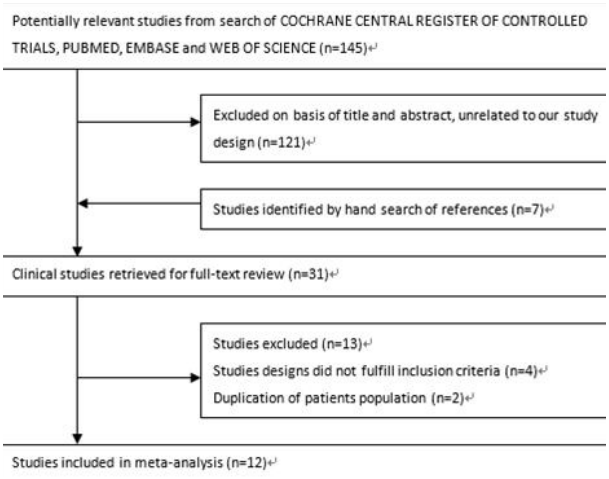


Figure 1. Flow Diagram of Study Selection

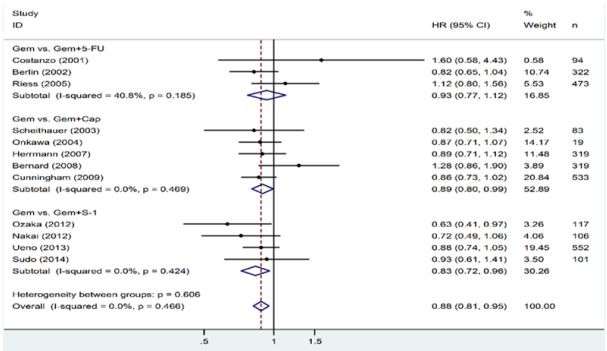


Figure 2. For the primary endpoint of OS, the gemcitabine-based combination therapy was observed significantly better outcome (FEM: pooled HR, 0.88; 95% CI, 0.81-0.95; p = 0.001) than gemcitabine in monotherapy

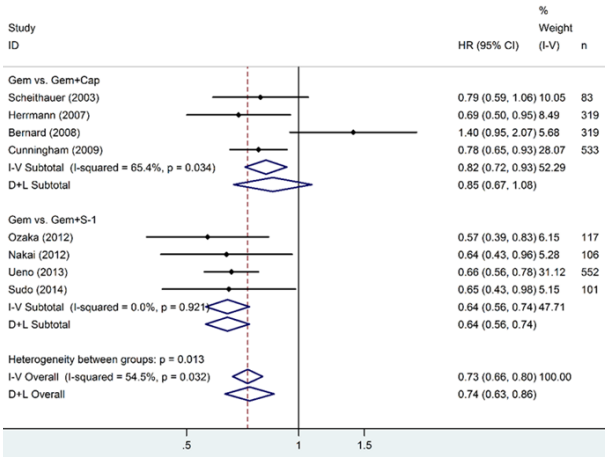


Figure 3. A significant result for the combined therapy in total 8 trials (2,130 patients) (REM: pooled HR=0.74; 95% CI, 0.63-0.86; p < 0.001; I^2=54.5%, p=0.032)

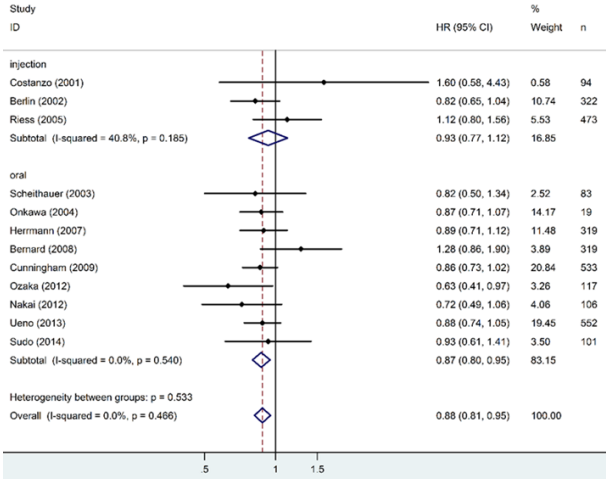


Figure 4. Trials Comparing Single-Agent Gemcitabine with Gemcitabine Combined Therapy in Different Dosing Delivery Ways

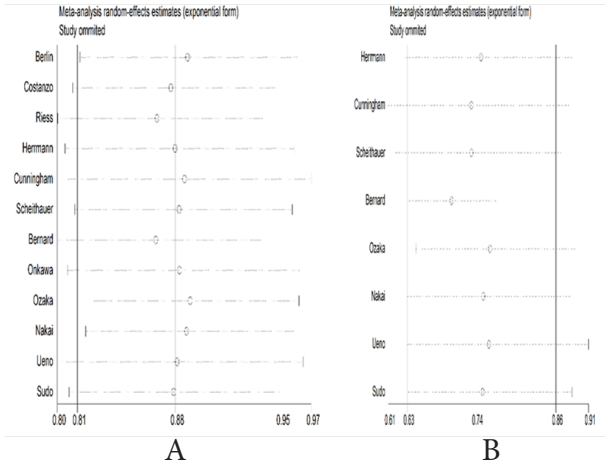
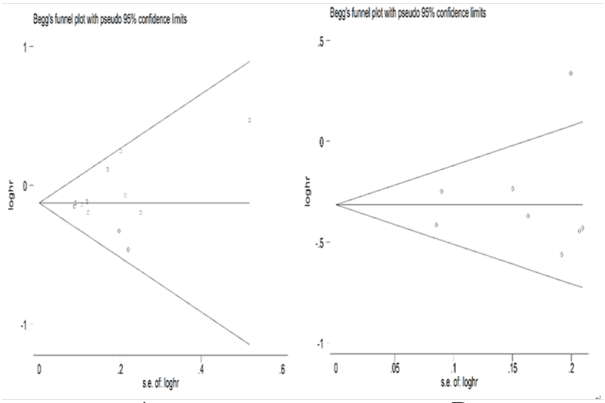


Figure 5. The Influence Analysis Results. A) The analysis for the primary endpoint of OS B) The analysis for the primary endpoint of PFS



A B

Figure 6. The Egger Funnel Plots Indicating Publication Bias for All Analysis. A) The analysis for the primary endpoint of OS B) The analysis for the primary endpoint of PFS

Influent analysis and publication bias evaluation

In the analysis for the primary endpoint of OS and PFS, there was no individual study substantially influencing the pooled HRs strongly forall the meta-analyses (Figure 5). In terms of publication bias, the shapes of the funnelplots were roughly symmetrical for the meta-analysis (Figure 6). There were no publication biasesdetected by Egger test for the studies in all of our analysis, in the primary endpoint of OS (t=0.74, p=0.474) and PFS (t=0.35, p=0.738) (Higgins et al., 2002; Higgins et al., 2003; Huai et al., 2013). Each article included in the composition of the funnel plot did not find significant bias (Berlin et al., 2002; Scheithauer et al., 2003; Ohkawa et al., 2004; Di Costanzo et al., 2005; Riess et al., 2005; Herrmann et al., 2007; Bernhard et al., 2008; Cunningham et al., 2009; Nakai et al., 2012; Ozaka et al., 2012; Ueno et al., 2013; Sudo et al., 2014).

Discussion

The treatment of APC (Advanced Pancreatic Cancer) with gemcitabine alone is considered the norm in current clinical practice worldwide. However, the role of gemcitabine-based combinationtherapy in the treatment of APC still remains to be elucidated (Bria et al., 2007; Ying et al., 2012). Furthermore, according to Domenico Ciliberto et al. (2013), patients have benefits when treated with gemcitabine-based combination therapy with fluoropyrimidine (HR=0.91), butno significant benefit in OS for gemcitabine-based combination therapy with platinum. We evaluated the impact ofgemcitabine-based combination therapy with fluoropyrimidineas comparedto gemcitabine alone by considering survival, in overall and subgroup evaluations, in anattempt to present the most complete analysis of currently available evidence.

5-Fluorouracil (5-FU), 5-fluoro-1H-pyrimidine-2, 4-dione, is anantimetabolite pyrimidine analogue. Before 1995, 5-FU was theonly drug with a response rate with an upper 95% confidence limitexceeding 20% before the CT was widely used. Prior to the approvalof gemcitabine in 1996, 5-FU was considered the standard chemotherapeutic treatment for advanced pancreatic cancer, showing awide range of response rates from 0% to 67% (Carter et al., 1975; Cullinan et al., 1985; Rougier et al., 1993; Ducreux et al., 2002; Haller et al., 2003; Strimpakos et al., 2008). Berlin et alfound that the median OS was 6.7months for GEM combined with 5-FU and 5.4 months for GEMalone, Di Costanzo's study depicted that the median OS was 7.7 months for GEM combined with 5-fu and 7.5 months for GEM alone, Riess et al. (2005) presented that the median OS was 5.85 monthsfor GEM combined with 5-FU and 6.2 months for GEMalone. However, in our study we could see there was no significantly better outcome in Group Gem *vs*. Gem + 5-FU (HR, 0.93; 95% CI, 0.77-1.12; p=0.451).

Capecitabine is an oral prodrug of 5-FU which is rationally designed to generate 5-FU preferentially within tumors. It is converted to 5-FU by three sequential enzymatic reactions. The lastenzyme, thymidine phosphorylase (TP), has a higher level in tumors than in healthy tissues and therefore makes capecitabinemore effective and specific in targeting tumors than 5-FU. Treatment with capecitabine showed promising clinical benefitson tumor-related symptoms and yielded objective response activity in patients with metastatic or locally advanced pancreatic cancer, suggesting capetabine might be a better option than 5-FU (Miwa et al., 1998; Cartwright et al., 2002; Choi et al., 2012). Herrmann et al. (2007) reported that the median OS was 8. 4 months for GEM combined with CAP and 7.2 months for GEM alone, Cunningham's study showed that the median OS was 8.4 months for GEM combined with CAP and 7.2 months for GEMalone. Scheithauer et al suggested that the median OS was 9.5 months for GEM combined with CAP and 8. 2 months for GEM alone. Onkawa's study presented that the median OS was 5 months for GEM combined with CAP and 7.6 months for GEMalone. In conclusion the significant results were found in Group Gem *vs*. Gem + Cap with 5 trials (HR=0.89; 95% CI, 0.80-0.99; p=0.038). The analysis of PFS also provided a significant result for the combined therapy in total 8 trials (2,130 patients) (REM: pooled HR=0.74; 95% CI, 0.63-0.86; p<0.001; I^2=54. 5%, p=0.032) (Figure 2). An advantage result for therapy Gem + Cap (4 trials including 1,254 patients) was observed in subgroup analysis (FEM: pooled HR, 0.64; 95% CI, 1.31-1.91; p<0.001).

In recent years, the efficacy of S-1 confirmed by the treatment of gastrointestinal tumors especially in gastric cancer has been widely recognized. One third of S-I is tegafur, which is one kind of precursor5-Futhat could be converted *in vivo* to5-FU, and better than 5-FU's bioavailability. Meanwhile, the left two-component Jigme pyrimidine and oteracil vivo stopped 5-Fu degradation process by inhibitingenzymatic reaction (Shirasaka et al., 1996; Ueno et al., 2005; Morizane et al., 2009; Satoh et al., 2012). Ozaka et al reported that the median OS for GEM combined with S-1 was 13.7 months and 8.0 months for GEM alone. Nakai et al. (2012) observed that the median OS for GEM combined with S-1 was 13.5 months and 8. 8 months for GEMalone. Ueno et al presented that the median OS for GEM combined with S-1 was 10.1 months and 8.8 months for GEMalone. Sudo et al. (2014) showed that the median OS for GEM combined with S-1 was 8.6 months and 8.6 months for GEMalone. And in our conclusion, we found that there was significantly better

outcome in Group Gem + S-1 *vs*. Gem (HR, 0.83; 95% CI, 0.72-0.96; p=0.011;). but the result was negative in Group Gem *vs*. Gem + S-1 with 4 trials (876 patients) (REM: pooled HR=0.85; 95% CI, 0.67-1. 08; p<0.076; I^2=65. 4%, p=0.034).

Traditional 5-FU therapy has been proved to have minimal effects on the disease, however, new oral fluoropyrimidines, such as capecitabine and S-1may provide more effective results. Trials comparing single-agent gemcitabine with gemcitabine combined therapy in different dosing delivery ways (Shi et al., 2012). When we conducted subgroup analysis according to the dosing delivery ways, we found different results in the two groups. In the injection group with 3 trials (889 patients), a negative result was found (FEM: pooled HR, 0.93; 95% CI, 0.77-1.12; p=0.451; I^2=40.8%, p=0.185); while a positive result was observed in oral group with 9 trials (2, 149 patients) (FEM: pooled HR, 0.87; 95% CI, 0.80-0.95; p=0.001; I^2=0.0%, p=0.540), showed in Figure 3.

However, this meta-analysis has some limitations. Firstly, it is ameta-analysis of published studies, with HRs for OS and PFS derived (or calculated) directly from publications or abstracts. Thus, formalsubgroup analyses, including adjustments for different baselinefactors such as age, stage of disease (locally advanced unresectable metastatic), site of primary disease (head *vs* others) or PS, amongthe trials included was not possible. Secondly, the trials included were only performedon Asian races, especially Japanese. Reports fromotherparts of the world were not available yet. Asmore severe toxicity of S-1 occurred in Europe and USthanin Asian patients (van Groeningen et al., 2000; Hoff et al., 2003), the results could notbesimply extrapolated to Western patients and more confirmations are needed. Compared to Li et al. (2014), we included a more comprehensive document, while increasing the oral and injectable subgroup analysis and thereby giving a more comprehensive and systematic analysis of the OS and PFS. But since there is an abscence of descriptions of needed parameters, we don't generalize the analysis of adverse reactions of drugs.

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