ORIGINAL RESEARCH

Combination therapy versus gemcitabine monotherapy in the treatment of elderly pancreatic cancer: a meta-analysis of randomized controlled trials

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Purpose: We aimed to compare the efficacy of combination therapy versus gemcitabine monotherapy in the treatment of elderly pancreatic cancer (PC) by using a meta-analysis.

Materials and methods: Databases were searched to identify relevant clinical trials. Hazard ratios (HRs) were used to estimate overall survival (OS) and progression-free survival (PFS). Statistical analyses were conducted by using Comprehensive Meta Analysis software (version 2.0).

Results: A total of 3,401 elderly PC patients from six randomized controlled trials were included for analysis. In comparison with gemcitabine alone, combination therapy in elderly PC patients did not significantly improve OS (HR 0.93, 95% CI: 0.82–1.06, $p=0.29$). Sub-group analysis according to treatment regimens showed that combined chemotherapy significantly improved OS in comparison with gemcitabine alone (HR 0.73, 95% CI: 0.56–0.94, $p=0.016$), while gemcitabine plus targeted agents did not improve OS (HR 1.02, 95% CI: 0.87–1.19, $p=0.83$). Additionally, gemcitabine plus nab-paclitaxel significantly improved PFS in elderly PC patients (HR 0.69, 95% CI: 0.52–0.91, $p=0.009$) in comparison with gemcitabine alone. No publication bias was detected by Begg's and Egger's tests for OS.

Conclusion: The findings of this study suggest that combined chemotherapy, but not for gemcitabine plus targeted agents, could be recommended for elderly PC patients due to its survival benefits. Further studies are still needed to assess the treatment tolerance of combination chemotherapy in these patient populations.

Keywords: pancreatic cancer, elderly, randomized controlled trials, meta-analysis, targeted agents

Introduction

Although pancreatic cancer (PC) accounts only for 3% of all new cancer cases, it is one of the most fatal malignancies.[1] Surgical resection with negative margins (R0) is the only potentially curative treatment for PC, but only 15%–20% of these patients are eligible for resection at the initial diagnosis, and the remaining 80%–85% of PC patients have metastatic or locally advanced disease.[2] Palliative therapies, such as chemotherapy and radiation, are the only therapeutic options for patients with metastatic or locally advanced PC, but the prognosis of these patients is dismal, with an overall 5-year survival rate <5%.[3] PC is generally a disease of the elderly, with a median age at diagnosis of 70 years, and 40% are diagnosed after the age of 75 years.[4] Currently, the number of the elderly in the world is rapidly increasing, and

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it is estimated that the number of elderly patients with PC will continue to increase. However, treatment of elderly PC patients may be complicated by several comorbid conditions and greater concomitant medication use when compared with younger patients. In addition, there are no available trials to specifically assess the role of combination therapy versus gemcitabine in elderly PC patients. As a consequence, there is an ongoing need to clearly investigate and determine the optimal treatment for PC in this patient group.

Single-agent gemcitabine, a pyrimidine antimetabolite and analog of deoxycytidine, has been approved by the Food and Drug Administration for the treatment of unresectable PC for many years, following a prospective randomized controlled trials of gemcitabine versus 5-fluorouracil (5-FU) conducted by Burris et al.[5,6] The authors in that study found that gemcitabine was more effective than 5-FU in the alleviation of some disease-related symptoms in patients with advanced, symptomatic PC. However, a large number of PC patients do not respond to gemcitabine due to high levels of intrinsic and acquired chemoresistance. To improve the clinical efficacy, gemcitabine-based combined therapy, often combined with a second cytotoxic agent such as platinum analogs,[7] fluoropyrimidine,[8,9] or a targeted cytotoxic agent,[10–12] has been extensively investigated in numerous clinical trials. Indeed, several prospective clinical trials have showed that gemcitabine-based combination therapy is superior over single-agent gemcitabine treatment, which is also confirmed by several meta-analyses of published data.[13–15] However, the efficacy and toxicities of combination therapy in elderly PC patients remain undetermined.

Currently, the concept of "elderly" has become more difficult to define. In general, the chronological age of 65 years – roughly equivalent to retirement age – is currently accepted as a threshold to define an "elderly" person. As the elderly PC population increases, it is urgently needed to define the best treatment strategy for these patients. In the present study, we assess the efficacy of combined therapy in the treatment of elderly PC patients by using age cutoffs of 65 years to determine whether aging might impact on the efficacy of combined therapy in this setting.

Materials and methods
Literature search strategy
We performed a comprehensive literature search for relevant trials, including PubMed (up to March 2017), Embase (up to March 2017), American Society of Clinical Oncology abstracts (up to March 2017), and the Cochrane Database (up to March 2017). The following keywords were used in the search: ("Gemcitabine" or "Gemzar") and ("pancreatic cancer" or "pancreatic tumor" or "pancreatic carcinoma") and ("elderly") and ("clinical trial"). The search was restricted to clinical trials published in English. The selection and systematic review of trials was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[16]

Definition of outcomes
Treatment with combined therapy was considered as the experimental arm, and treatment with the single-agent gemcitabine was regarded as the standard comparator. The outcomes used were 1) overall survival (OS), defined as the time from random assignment to death from any cause, censoring patients who were alive at the date of documenting and 2) progression-free survival (PFS), defined as the time from random assignment to first documented progression.

Inclusion and exclusion criteria
Trials 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 pancreatic ductal adenocarcinoma; and 3) assessment of the efficacy of gemcitabine combination therapy versus gemcitabine alone in elderly patients. Nonrandomized trials and quasi-randomized trials, and studies where patients had multiple cancers, were excluded to avoid clinical heterogeneities between different trials.

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

Quality assessment
We used the Jadad score to roughly assess the quality of the included trials. There were three items (randomization, double blinding, withdrawals, and dropouts) directly related to bias reduction for assessment. Each item was given a score of 1 point for each "yes" or 0 point for each "no", and 1 additional point for appropriate randomization and double blinding. Every eligible study was assessed and given a score from 0 to 5.

Statistical method

Statistical analysis of the overall hazard ratio (HR) for OS and PFS were performed by using version 2 of the Comprehensive Meta Analysis program (Biostat, Englewood, NJ, USA). A statistical test with a p-value of <0.05 was considered significant. HR >1 reflected more deaths or progression in combination therapy, and vice versa. Between-study heterogeneity was estimated using the χ^2-based Q statistic.[17] The I^2 statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials. The presence of publication bias was evaluated by using the Begg's and Egger's tests.[18] A statistical test with a p-value of <0.05 was considered statistically significant. All p-values were two sided. All CIs had a two-sided probability coverage of 95%.

Results

Our search yielded 150 relevant clinical studies investigating chemotherapy in PC patients. After excluding review articles, Phase I and II studies, case reports, and meta-analyses, we selected six prospective randomized controlled trials (RCTs)[10,19–23] (Figure 1). A total of 3,401 elderly PC patients were included for analysis. The characteristics of patients and studies are listed in Table 1. The quality of each study was roughly assessed according to Jadad scale. Two RCTs were randomized placebo-controlled trials and thus had a Jadad score of 5, and the other four RCTs were open-label randomized controlled trials and thus had a Jadad score of 3.

Progression-free survival

Only one trial conducted by Von Hoff et al[21] reported PFS data of elderly PC patients. The results in that study showed

Figure 1 Studies eligible for inclusion in the meta-analysis.
Abbreviation: PC, pancreatic cancer.

that gemcitabine plus nab-paclitaxel significantly improved PFS in elderly PC patients (HR 0.69, 95% CI: 0.52–0.91, p=0.009) in comparison with gemcitabine alone.

Overall survival

All of the six trials reported OS data of elderly PC patients. The pooled results demonstrated that combination therapy in elderly PC patients did not significantly improve OS (HR 0.93, 95% CI: 0.82–1.06, p=0.29, Figure 2). There was moderate heterogeneity between trials (I^2=57.5%, p=0.038), and the pooled HR for OS was performed by using random-effects model. Subgroup analysis according to treatment regimen showed that combined chemotherapy significantly improved OS in comparison with gemcitabine alone (HR 0.73, 95% CI: 0.56–0.94, p=0.016), while gemcitabine plus targeted agents did not improve OS (HR 1.02, 95% CI: 0.87–1.19, p=0.83).

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The Begg's funnel plots did not reveal any evidence of obvious asymmetry (p=0.71, Figure 3). Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias for OS (p=0.41).

Discussion

PC is a lethal malignant neoplasm with poor prognosis. Due to the introduction of new cytotoxic and targeted drugs in PC patients over the past 10 years, a significant survival benefit has been obtained from combined therapy when compared with gemcitabine alone. Two recently published meta-analyses showed that gemcitabine-based combination therapy significantly improved OS and PFS in comparison with single-agent gemcitabine.[24,25] Another two meta-analyses also showed that gemcitabine plus anti-epidermal growth factor receptor (anti-EGFR) therapy significantly improved OS and PFS when compared with gemcitabine alone.[26,27] However, whether combined therapy in elderly PC patients would improve survival remains undetermined. We, therefore, conduct this meta-analysis of RCTs with preplanned and unplanned subset analysis of elderly patients to investigate the overall efficacy of combined therapies in the treatment of PC in this setting.

Our systematic review is, to the best of our knowledge, the first systematic review to specially assess the efficacy of combined therapy in the treatment of elderly PC patients. Our study includes a total of 3,401 elderly PC patients. Compared with gemcitabine alone, combination therapy in elderly PC
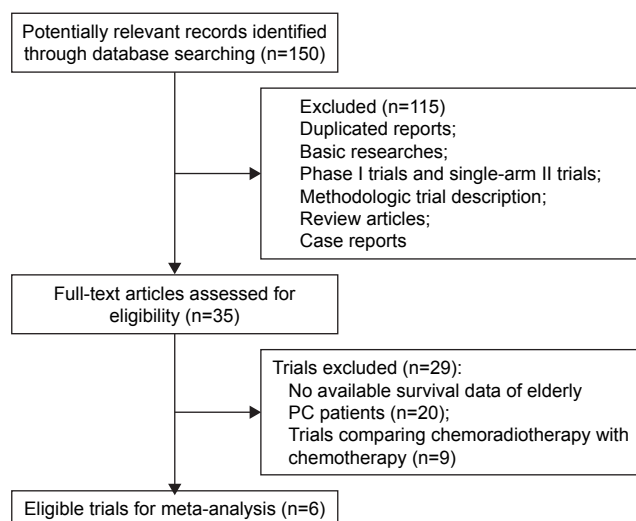
Table 1 Baseline characteristics of included trials

Authors/year	Phase	Total	Age (years)	No of elderly patients	Treatment arms	Median age (years)	Median PFS	Median OS	Jadad score
Moore et al/2007[10]	III	569	≥65	268	Gemcitabine + erlotinib	63.7	3.75	6.24	5
					Gemcitabine + placebo	64	3.55	5.91	
Conroy et al/2011[23]	III	342	≥65	98	FOLFIRINOX	61	6.4	11.1	3
					Gemcitabine	61	3.3	6.8	
Rougier et al/2013[22]	III	546	≥65	206	Gemcitabine + aflibercept	62	3.7	6.5	5
					Gemcitabine + placebo	61	3.7	7.8	
Von Hoff et al/2013[21]	III	861	≥65	365	Gemcitabine + nab-paclitaxel	62	5.5	8.5	3
					Gemcitabine	63	3.7	6.7	
Deplanque et al/2015[20]	III	353	≥65	NR	Gemcitabine + masitinib	62.6	NR	7.7	3
				NR	Gemcitabine	61.7	NR	7.1	
Neoptolemos et al/2017[19]	III	730	≥65	348	Gemcitabine + capecitabine	65	13.9	28	3
					Gemcitabine	65	13.1	25.5	

Abbreviations: FOLFIRINOX, oxaliplatin + irinotecan + fluorouracil + leucovorin; NR, not reported; OS, overall survival; PFS, progress-free survival.

patients does not significantly improve OS (HR 0.93, 95% CI: 0.82–1.06, p=0.29). There is moderate heterogeneity among the included trials, and most likely due to the pooling of studies across different modes of action (tyrosine-kinase inhibitors, cytotoxic agents, and monoclonal antibodies) and hence different magnitudes of effect. As a result, we perform a subgroup analysis according to treatment regimens and find that combined chemotherapy significantly improves OS in comparison with gemcitabine alone (HR 0.73, p=0.016), while gemcitabine plus targeted agents does not improve OS (HR 1.02, p=0.83) when compared with gemcitabine alone. Additionally, gemcitabine plus nab-paclitaxel significantly improves PFS in elderly PC patients (HR 0.69, p=0.009) in comparison with gemcitabine alone. Based on our findings, novel targeted agents are still needed to improve the OS of PC patients. Recently, Prabhu et al[28] found that protein arginine methyltransferase (PRMT) 5 is highly expressed in PC and is associated with disease progression. These authors

also discovered a novel small-molecule inhibitor targeting PRMT 5 showing higher antitumor efficacy than commercial PRMT 5 inhibitors, which might be a promising novel targeted agent in the near future. Overall, our study demonstrates a survival benefit of combined chemotherapy over gemcitabine alone in the treatment for advanced PC patients, but not for gemcitabine combined with novel targeted agents. None of the included trials reported the toxicities associated with combined therapy in PC, and thus, further studies are still needed to investigate the role of combined chemotherapy in this patient population.

Several limitations exist in this analysis. First of all, this is a meta-analysis at study level, but not a meta-analysis of individual patient data. Thus, we could not incorporate patients' variables into the analysis. For instance, elderly patients are more likely to have comorbid conditions, but we are unable to investigate whether the survival benefit is similar in elderly patients with or without comorbid conditions. Second, none
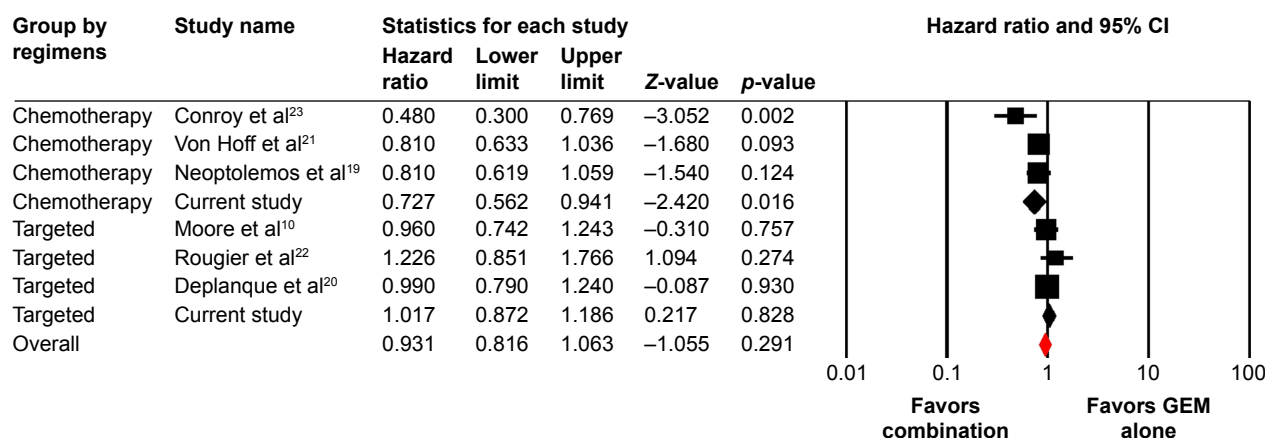
Group by regimens	Study name	Hazard ratio	Lower limit	Upper limit	Z-value	p-value
Chemotherapy	Conroy et al[23]	0.480	0.300	0.769	−3.052	0.002
Chemotherapy	Von Hoff et al[21]	0.810	0.633	1.036	−1.680	0.093
Chemotherapy	Neoptolemos et al[19]	0.810	0.619	1.059	−1.540	0.124
Chemotherapy	Current study	0.727	0.562	0.941	−2.420	0.016
Targeted	Moore et al[10]	0.960	0.742	1.243	−0.310	0.757
Targeted	Rougier et al[22]	1.226	0.851	1.766	1.094	0.274
Targeted	Deplanque et al[20]	0.990	0.790	1.240	−0.087	0.930
Targeted	Current study	1.017	0.872	1.186	0.217	0.828
Overall		0.931	0.816	1.063	−1.055	0.291

Figure 2 Random-effects model of hazard ratio (95% CI) of OS in elderly breast cancer patients treated with combined therapy versus gemcitabine alone.
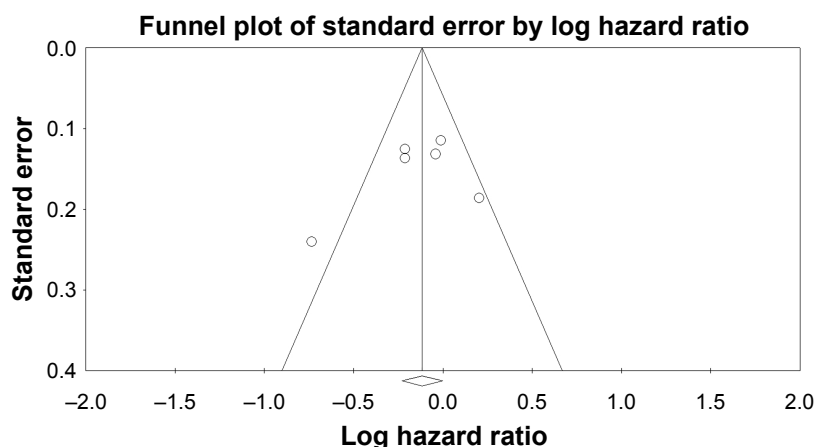**Abbreviations:** GEM, gemcitabine; OS, overall survival.

Figure 3 Funnel plot for publication bias.

of the included trials report the toxicities of combination therapy in elderly PC patients. Thus, we could not answer whether combination therapy in this patient population would increase the toxicities in comparison with gemcitabine alone. Third, there is moderate heterogeneity among the included studies due to different treatment regimens included for analysis, although we perform subgroup analysis according to treatment regimens. Fourth, there is still no general agreement on the definition of elderly population. In the present study, all of the included trials define elderly patients as >65 years. Finally, in a meta-analysis of published studies, publication bias is important because trials with positive results are more likely to be published and trials with null results tend not to be published. In the present study, we detect no publication bias using Begg's and Egger's tests for OS.

Conclusion

Although the present study has described several limitations, this meta-analysis, for the first time, demonstrates that combined chemotherapy significantly improved OS in elderly PC patients when compared with gemcitabine monotherapy, but not for gemcitabine combined with targeted agents. Further trials are needed to investigate the treatment tolerance of combination chemotherapy in elderly PC patients.

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Disclosure

The authors report no conflicts of interest in this work.

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