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Clinical efficacy and safety of erlotinib combined with chemotherapy in the treatment of advanced pancreatic cancer: A meta-analysis

INTRODUCTION

Pancreatic cancer is one of the most common malignant gastrointestinal tumors worldwide, and its incidence and mortality rates are increasing each year[1]. The current mainstay of pancreatic cancer treatment is surgical resection, and early surgery has been shown to increase the likelihood of successful resection, with postoperative 5-year survival rates ranging from 70% to 85%[2]. However, pancreatic tumors tend to infiltrate surrounding tissues, and early detection and metastasis prevention pose significant challenges. Consequently, most pancreatic cancers are diagnosed at advanced stages. Only 10% of advanced pancreatic cancers can be surgically resected, resulting in a 5-year survival rate of less than 4%[3]. As such, systemic chemotherapy is the primary treatment for pancreatic cancer. However, despite the efficacy of cytotoxic drugs in inducing tumor cell apoptosis, the abnormal permeability of blood vessels surrounding the tumor tissue diminishes the influx of chemotherapeutic agents into the tumor. Furthermore, residual tumor cells can acquire essential growth-promoting substances from the surrounding blood supply, which enables continued proliferation, ultimately limiting the efficacy of chemotherapeutic drugs. This underscores the urgent need for novel and effective approaches.

The evolving fields of molecular biology and tumor immunology have paved the way for targeted drug therapy for pancreatic cancer at the molecular level. This approach allows the design of drugs that selectively act on oncogenic sites within the body,

inducing tumor cell-specific death while sparing normal tissue cells surrounding the tumor[4,5]. Erlotinib is a tyrosine kinase inhibitor (EGFR antagonist) used as a molecularly targeted therapeutic drug that competitively binds to the catalytic site of the intracellular region of the tyrosine kinase receptor with adenosine triphosphate, inhibiting the phosphorylation reaction. This, in turn, blocks downstream proliferative signaling and hinders ligand-dependent HER-1/EGFR activity in tumor cells, ultimately suppressing tumor cell proliferation[6,7]. When used in conjunction with chemotherapeutic drugs for pancreatic cancer treatment, erlotinib has demonstrated favorable outcomes. Hence, this study aimed to evaluate the clinical efficacy and safety of erlotinib monotherapy combined with chemotherapy for the treatment of advanced pancreatic cancer, with the goal of offering valuable insights into the clinical management of this disease.

MATERIALS AND METHODS

Literature search

Literature searches were conducted in the PubMed, Embase, and Cochrane Library databases from inception to November 2023. The search terms used were "pancreatic cancer", "pancreatic adenocarcinoma", "erlotinib", "gemcitabine", "Erlotinib monotherapy combined with chemotherapy", "advanced pancreatic cancer", *etc.*

Inclusion and exclusion criteria

The inclusion criteria were: (1) Randomized controlled trials published in English; (2) studies conducted in patients with pathologically diagnosed advanced pancreatic cancer; (3) studies where patients in the control group were treated with chemotherapeutic drugs (gemcitabine and capecitabine) and those in the observation group were treated with erlotinib combined with chemotherapy; and (4) studies that assessed disease control rate (DCR), overall survival (OS), and progression-free survival (PFS) as efficacy indices. Articles that met the following criteria were excluded: (1)

retrospective studies; (2) studies with incomplete data; and (3) case reports and news articles.

Extraction of the literature

The literature was screened by two professionals, and relevant data were extracted. The screened information was cross-checked and disagreements were resolved by discussion with a third author. The extracted information primarily included the (1) article title, literature source, authors, and publication date; (2) literature type and relevant elements for assessing the risk of bias; (3) interventions provided to the control and study groups, patients' age, *etc.*; and (4) outcome indicators found in the literature, which included efficacy (DCR, PFS, and OS) and adverse effects (diarrhea, rash, vomiting, regurgitation/anorexia, and infection).

Evaluation of the quality of the literature

The Cochrane International Collaboration was used to evaluate the quality of the literature based on the sequence of randomization, allocation concealment, blinding implementation, presence of other biases, patient withdrawals, and loss to follow-up[8].

Statistical analysis

A meta-analysis of the efficacy and safety of erlotinib monotherapy in combination with chemotherapy for advanced pancreatic cancer was performed using RevMan 5.3 software. Dichotomous variables were evaluated as relative risks (RRs) or odds ratios (ORs) and 95%CIs for the effect analysis. For continuous variables, the mean, standard deviation, and 95%CI were used as effect statistics. Measurement data were compared using the chi-square test and combined with I^2 values for the size of heterogeneity, where a P value of > 0.10 and an I^2 value of < 50% indicated good statistical homogeneity. Meta-analysis was performed using a fixed-effects model, with a P value of ≤ 0.10 and an I^2 value of ≥ 50% indicating the presence of statistical heterogeneity. Finally, a meta-analysis was performed using a random-effects model. If the screened

literature data were not subjected to meta-analysis, a descriptive analysis was performed.

RESULTS

Results of the literature search

The literature search and screening processes are depicted in Figure 1. Initially, 806 papers were retrieved by searching the databases of related websites using relevant keywords. After Endnote processing, 178 duplicates were removed, leaving 628 papers for further consideration. Subsequently, the titles and abstracts of conference papers, reviews, case reports, non-randomized controlled trials, and duplicate publications were screened, resulting in the exclusion of an additional 393 articles. Finally, 235 articles were retained for further examination. After reading these articles, 225 were excluded, resulting in the inclusion of 10 articles in the final analysis.

Baseline characteristics of studies included in the literature

Ten articles[9-18], all of which were randomized controlled trial studies, published between 2007 and 2020, with a total sample size of 2444 patients, were screened. The patients in the control group were treated with gemcitabine, capecitabine, or gemcitabine, whereas those in the study group were treated with gemcitabine or erlotinib. Characteristics of the included studies are listed in Table 1.

Literature quality assessment

The included studies exhibited a low risk of bias in terms of randomized sequence methods, blinding of literature results, and selective reporting. The overall quality of the studies was rated as B (Figure 2).

Meta-analysis results of DCR

Five[9-11,13,16] of the 10 included articles reported DCR, including 509 patients in the control group and 585 patients in the study group. Statistical heterogeneity was

observed among studies (P = 0.0001, I^2 = 83%). Therefore, using a random-effects model, a meta-analysis showed that there was no significant difference in the DCR between the two groups of patients [OR = 0.93 (0.45–1.91), P = 0.84] (Figure 3A).

Meta-analysis results of OS

All 10 studies[9-18] reported the effect of erlotinib combination chemotherapy on OS in patients with pancreatic cancer, including 1258 patients in the control group and 1186 patients in the study group. Statistical heterogeneity was observed among the studies (P < 0.0001, I^2 = 92%). Using a random-effects model, a meta-analysis showed that there was no significant difference in the comparison of OS between the two groups of patients [HR = 0.99 (0.72–1.37), P = 0.95] (Figure 3B).

Results of the meta-analysis of PFS

All 10 studies[9-18] reported the effect of erlotinib combination chemotherapy on PFS in patients with pancreatic cancer, including 1258 patients in the control group and 1186 patients in the study group. Significant heterogeneity was observed among the studies (P < 0.0001, I^2 = 73%). Using a random-effects model, the meta-analysis showed that the study group had significantly prolonged PFS compared with the control group (P < 0.001, Figure 3C).

Adverse reactions

Results of the meta-analysis of diarrhea incidence: Three studies[12,13,16] reported the incidence of diarrhea, and no statistical heterogeneity was found (P > 0. 05, I^2 = 0%). Hence, they were analyzed using a fixed-effects model. Results showed that the incidence of diarrhea in the study group was 3.59 times higher than that in the control group, and this difference was significant (P < 0. 001; Figure 4A).

Results of the meta-analysis of rash incidence: Three studies[13,16,17] reported the incidence of rash, but no statistical heterogeneity was found (P > 0.05, I^2 = 0%). Hence,

these studies were analyzed using a fixed-effects model. Results showed that the incidence of rash in the study group was 3.63 times higher than that in the control group, and this difference was significant ($P < 0.001$; Figure 4B).

Results of the meta-analysis of vomiting incidence: Four studies[12,13,16,17] reported on the incidence of vomiting, among which no statistical heterogeneity was found ($P > 0.05$, $I^2 = 0$%); therefore, they were analyzed using a fixed-effects model. Results showed that the incidence of vomiting in the study group was 1.27 times higher than that in the control group. However, this difference was not statistically significant ($P > 0.05$; Figure 4C).

Meta-analysis results of regurgitation/anorexia: Three studies[12,16,17] reported the incidence of regurgitation/anorexia, among which a statistical heterogeneity was observed ($P < 0.05$, $I^2 = 85$%); hence, these studies were analyzed using a random-effects model. Results showed that the incidence of regurgitation/anorexia was 1.60 times higher in the study group than that in the control group, but the difference was not significant ($P > 0.05$, Figure 4D).

Results of the meta-analysis of infection incidence: Two studies[13,16] reported the incidence of infections, and statistical heterogeneity was observed ($P > 0.05$, $I^2 = 0$%). Therefore, they were analyzed using a fixed-effects model. The results showed that the incidence of infection in the study group was 0.72 times higher than that in the control group; however, the difference was not statistically significant ($P > 0.05$, Figure 4E).

Publication bias: Funnel plots were constructed based on the clinical efficacy and safety of erlotinib monotherapy combined with chemotherapy for advanced pancreatic cancer, and showed good symmetry on both sides of the funnel plots with less publication bias (Figure 5).

DISCUSSION

Most patients with pancreatic cancer are diagnosed at an intermediate or advanced stage, with radical surgery considered feasible in only 15% to 20% of patients; however, the rates of recurrence and metastasis are high after surgery[19,20]. Therefore, patients with intermediate or advanced pancreatic cancer, as well as those who undergo radical surgery require further intervention. Novel pharmacological mechanisms of action for molecularly targeted drugs have garnered the attention of the medical community in recent years, leading to their rapid development. Erlotinib is a novel epidermal growth factor receptor tyrosine kinase inhibitor that can be orally administered. It effectively inhibits EGFR and blocks intracellular tyrosine kinase phosphorylation. The overexpression or mutation of EGFR in many tumors can lead to uncontrolled cell growth and malignancy. Erlotinib inhibits tumor cell proliferation, invasion, and metastasis by blocking EGFR, promoting apoptosis, enhancing sensitivity to chemotherapy, and improving the therapeutic effects. Erlotinib inhibits EGFR; hinders tumor cell proliferation, invasion, and metastasis; promotes tumor cell apoptosis; enhances sensitivity to chemotherapy; improves therapeutic effects; and prolongs the survival of patients with tumors[21,22]. However, whether erlotinib combined with chemotherapeutic drugs has significant advantages over chemotherapeutic drugs alone in the treatment of pancreatic cancer currently remains unclear. Hence, we conducted a meta-analysis of existing clinical studies to compare the efficacy and safety of erlotinib combined with chemotherapeutics and chemotherapeutic drugs alone for the treatment of pancreatic cancer.

Although molecularly targeted agents exhibit good clinical efficacy in the treatment of pancreatic cancer, the results of published clinical studies vary significantly. Moore *et al*[11] conducted a phase III clinical randomized controlled trial (RCT) and randomized 569 patients with locally progressive or distant metastatic pancreatic cancer into two groups in a 1:1 ratio. One group received erlotinib in combination with gemcitabine, while the other received gemcitabine alone. Results showed median OS rates of 6.24 months and 5.91 months in these groups ($P = 0.038$), respectively, with the combination

therapy showing a better survival benefit than single-agent gemcitabine. Despite the positive results of this study, the survival benefit in the trial group was extremely limited and inconsistent with the conclusions of several subsequent prospective clinical RCTs. In a phase III clinical RCT, the LAP07 study, published in 2016, Hammel *et al*[12] enrolled 442 patients with locally progressive pancreatic cancer. Trial and control groups were treated with erlotinib in combination with gemcitabine or gemcitabine alone, respectively. Results showed that the median OS durations of the two groups were 11.9 and 13.6 months, respectively (P = 0.09), and the difference was not significant. Nevertheless, the results of this study showed that erlotinib combined with chemotherapy significantly prolonged the PFS of pancreatic cancer patients compared with chemotherapy alone (HR = 0.78, 95%CI: 0.66–0.92, P = 0.003). This finding indicates that erlotinib combined with chemotherapy can help patients stabilize their disease and prolong the progression-free time of pancreatic cancer. However, this combination treatment had no significant benefits on OS (HR = 0.99, 95%CI: 0.72–1.37, P = 0.95) or DCR (OR = 0.93, 95%CI: 0.45–0.91, P = 0.84). Second, in terms of safety, erlotinib combined with gemcitabine increased the risk of diarrhea (OR = 3.59, 95%CI: 1.63–7.90, P < 0.05) and rash (OR = 3.63, 95%CI: 1.64-8.01, P < 0.05) in patients with advanced pancreatic cancer compared with single-agent chemotherapy, which is not conducive to the stabilization of the disease and recovery. Although the risk of vomiting (OR = 1.27, 95%CI: 0.62-2.59, P = 0.51), regurgitation/anorexia (OR = 1.61, 95%CI: 0.25–10.31, P = 0.62), and infection (OR = 0.72, 95%CI: 0.28–1.87, P = 0.50) occurred in the two groups of patients, the difference was not significant. This observation indicates that erlotinib combination chemotherapy did not increase the risk of vomiting, regurgitation/anorexia, or infection in patients with advanced pancreatic cancer compared with single-agent chemotherapy. Moreover, the included studies exhibited good baseline comparability, and the meta-analysis was well-standardized. The symmetry on both sides of the funnel plots of DCR, OS, PFS, and adverse effects in patients after treatment indicated that publication bias had minimal impact on the study results and that the outcomes maintained a high level of confidence. Therefore,

the results of this meta-analysis are reliable and stable, providing an evidence-based reference for the clinical treatment of advanced pancreatic cancer, and guiding further research.

This study had several limitations which should be mentioned. Firstly, the literature search was limited to articles published in English, only a few RCTs were included, and the sample sizes of the included studies were small. Secondly, the tumor stages of all included patients in the original studies differed or lacked relevant information. Furthermore, differences existed in the scoring criteria used to assess the physical status of included patients, with variations either between studies or due to the absence of data on the physical status of patients in the original studies. Further, the duration of follow-up between the included studies considerably varied. Finally, some of the studies do not provide relevant information; for example, only two papers mention infections in the results of adverse reactions. Given the above clinical and methodological heterogeneity and the small sample size used in the stratified analysis, the conclusions of this study need to be verified further in the clinical setting.

Systematic evaluation enables the analysis and assessment of existing clinical studies, provides guidance for clinical practice, and suggests directions for future research. Several suggestions can be made based on the limitations of this study. The process of reporting RCTs should be standardized, especially the description of methodological quality, the endpoints should be described in detail, the follow-up and recording of safety and long-term efficacy indicators should be strengthened, the economic indicators related to the report should be collected in order to make it is easier to evaluate the economic aspects of the interventions, and more high-quality, large-sample clinical studies should be conducted to validate the conclusions of this meta-analysis. Additional high-quality large-sample clinical studies are required to validate the findings of this meta-analysis. The use of erlotinib in combination with other chemotherapeutic agents to improve patient outcomes remains an important topic in clinical research.

CONCLUSION

Overall, the results of the present meta-analysis show that, in contrast to single-agent chemotherapy, the combination of erlotinib and chemotherapy prolongs PFS in patients with pancreatic cancer. Furthermore, it does not elevate the risk of vomiting, regurgitation/anorexia, or infections in patients with advanced pancreatic cancer. However, this combination does not enhance survival benefits or DCR and may increase the risk of diarrhea and rash.

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Figure Legends

Figure 1 Flowchart showing the process and results of the literature screening.

Figure 2 Literature bias evaluation chart.

Figure 3 Forest plot of the meta-analysis of disease control rate, overall survival, and progression-free survival in the two groups. A: Disease control rate; B: Overall survival; C: Progression-free survival.

Figure 4 Forest plot of the meta-analysis comparing the incidence of adverse reactions in the two study groups. A: Incidence of diarrhea; B: Incidence of rashes; C: Incidence of vomiting; D: Regurgitation/anorexia; E: Infections.

Figure 5 Plot of publication bias. A: Funnel plot depicting publication bias in the literature reporting disease control rate; B: Funnel plot depicting publication bias in the literature reporting overall survival; C: Funnel plot of publication bias in the literature reporting the incidence of progression-free survival; D: Funnel plot of publication bias in the literature reporting the incidence of regurgitation of anorexia nervosa; E: Inverted funnel plot of publication bias in the literature reporting the incidence of vomiting; F: Inverted funnel plot of publication bias in the literature reporting the incidence of diarrhea; G: Inverted funnel plot of publication bias in studies reporting the incidence of infections; H: Inverted funnel plot of publication bias in studies reporting the incidence of rashes.

Table 1 Baseline characteristics of studies included in the meta-analysis

Ref.	Vintages	Number of examples		M/F		Age/yr		Intervention		Observation indicators
		Control patients	Research group	Control patients	Research group	Control patients	Research group	Control patients	Research group	
Takahashi et al[9]	2014	202	102	-	-	-	-	Gemcitabine (loanword)	Gemcitabine + erlotinib	1, 2, 3
Wang et al[10]	2015	44	44	33/11	32/12	-	-	Gemcitabine (loanword)	Gemcitabine + erlotinib	1, 2, 3
Moore et al[11]	2007	284	285	162-122	136/149	64 (36.1–92.4)	63.7 (37.9–84.4)	Gemcitabine + placebo	Gemcitabine + Erlotinib	1, 2, 3
Hammel et al[12]	2016	223	219	117/106	111/108	64 (57–70)	63 (58–71)	Gemcitabine (loanword)	Gemcitabine + erlotinib	2, 3, 4, 6, 7
Jeon et al[13]	2012	19	34	14/5	20/14	58 (48–70)	59.5 (35–73)	Gemcitabine + capecitabine	Gemcitabine + erlotinib	1, 2, 3, 4, 5 ,6, 8
Abrams et al[14]	2020	163	167	88/75	96/63	-	-	Gemcitabine (loanword)	Gemcitabine + erlotinib	2, 3
Sinn et al[15]	2017	217	219	119/98	128/91	65 (24–82)	63 (28–82)	Gemcitabine (loanword)	Gemcitabine + erlotinib	2, 3
Lim et al[16]	2015	36	44	25/11	25/19	68 (41–84)	63 (32–78)	Gemcitabine + capecitabine	Gemcitabine + erlotinib	1, 2, 3, 4, 5, 6, 7, 8
Halfdanarson et al[17]	2019	46	46	29/17	31/15	Median age: 60.5	Median age: 62	Gemcitabine (loanword)	Gemcitabine + erlotinib	2, 3, 5, 6, 7
Chun et al[18]	2011	18	26	-	-	Median age:	Median age:	Gemcitabine +	Gemcitabine + erlotinib	2, 3

	57.67 years	56.58 years	capecitabine

1: Disease control rate; 2: Overall survival; 3: Progression-free survival; 4: Diarrhea; 5: Skin rash; 6: Vomiting; 7: Regurgitation/anorexia; 8: Infection.

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SIMILARITY INDEX

PRIMARY SOURCES

1   Leyang Liu, Zhe Liu, Beibei Duan, Qianghuizi Zhang, Zheyi Zhou, Weiwei Liu. "Effects of a low glycemic index or low glycemic load diet on pregnant women at high risk of gestational diabetes: A meta-analysis of randomized controlled trials", Nutrition, Metabolism and Cardiovascular Diseases, 2023   78 words — 3%
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