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Meta analysis of gemcitabine plus nab-paclitaxel combined with targeted agents in the treatment of metastatic pancreatic cancer

Li ZH *et al.* Metastatic pancreatic cancer, gemcitabine, nab-paclitaxel, novel targeted agent, survival

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Abstract

BACKGROUND

Gemcitabine plus nab-paclitaxel (GA) is the commonly used first-line treatment regimen for metastatic pancreatic cancer, and many studies will add a novel targeted agent to this regimen for furtherly improving patient survival rate. However, the clinical effectiveness of GA is the most controversial issue.

AIM

To compare the efficacy and safety of GA regimen with a targeted agent and GA regimen.

METHODS

Up to 1 December 2021, the eligible randomized controlled trials relating to GA and GA with a targeted agent were searched on PubMed, EMBASE and Cochrane for eligible data. We screened out appropriate studies for overall survival (OS), progression-free survival (PFS), objective response rates (ORR), and toxicity rates (TRs) which had been pooled and finally analyzed by using Stata version 15.1.

RESULTS

A total of 7 randomized controlled trials involving 1544 patients (848 men and 696 women) were included. According to the results, there was no significant differences

between GA with a targeted agent and GA in PFS (HR: 1.18 95%CI: 0.91-1.53), OS (HR: 1.12 95%CI: 0.99-1.27), and ORR (HR: 0.96 95%CI: 0.71-1.29). There was no notable difference in the two groups in Grade 3/4 TRs (fatigue, anemia, vomiting and neutropenia), whereas the incidence of grade 3/4 diarrhea considerably increased in GA with a targeted drug.

CONCLUSION

Adding a novel targeted agent in the GA regimen did not improve survival rate of patients with metastatic pancreatic cancer.

Key Words: Metastatic pancreatic cancer; Gemcitabine; Nab-paclitaxel; Novel targeted agent; Survival

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Core Tip: Gemcitabine plus nab-paclitaxel (GA) is a commonly used first-line treatment regimen for metastatic pancreatic cancer, and many studies will add a novel targeted agent to this regimen to further improve patient survival. However, the clinical effectiveness of GA is more controversial. We conducted a meta-analysis to compare the effectiveness and safety of GA combined with a targeted agent regimen and GA regimen.

INTRODUCTION

Pancreatic cancer is a highly malignant malignancy with annual incidence rates ranging from 0.5 to 1.0 percent[1] meanwhile, one study predicts that by 2040 the pancreatic cancer will be the second most common cause of cancer-related deaths in the United States[2]. The current treatment outcome of pancreatic cancer is still not in ideal situation, and the more important reason is the shortage of effective screening and diagnosing modalities,

which causes most patients already in locally advanced (30%-35%) or metastatic (50%-55%) stage when diagnosed. In addition, surgery is the only treatment modality to cure pancreatic cancer, whereas 80%-85% of pancreatic cancer patients have missed the opportunity for surgical resection when diagnosed[3]. Even if surgical treatment improves patient outcomes, the 5-year survival rate is still less than 10%[4]. Currently, gemcitabine and albumin combined with paclitaxel or modified FOLFIRINOX (fluorouracil, calcium folinate, irinotecan and oxaliplatin) are the standard regimen for treating metastatic pancreatic cancer. According to the results of a phase III study on 861 patients with metastatic pancreatic cancer, Von Hoff *et al*[5] showed that gemcitabine plus nab-paclitaxel (GA) had a higher survival rate than single-agent gemcitabine (median survival 8.5 *vs* 6.7 mo; HR: 0.72 95%CI: 0.62-0.83; $P < 0.001$).

The effectiveness of GA has been fully demonstrated by its widely application in clinical practice and systematic analysis[6], However, systematic analyses for effectiveness and safety in GA and FOLFIRINOX showed that FOLFIRINOX has longer median overall survival (OS) and few difference in the overall risk of death and progression between FOLFIRINOX and GA[7]. Besides more previous studies evaluating gemcitabine compared with gemcitabine combination, and the results of meta-analysis indicated that gemcitabine combined with targeted drugs did not improve OS and progression-free survival (PFS) in patients compared with gemcitabine alone[8], Nevertheless, there has been no meta-analysis on whether GA regimens can improve effectiveness when combined with a targeted drug.

In clinical settings, targeted medicines with distinct modes of action, which could dramatically increase patients' survival rate, play a critical role in cancer treatment. For instance, tarextumab, a novel anti-cancer stem cell antibody against Noch2/3, has been demonstrated to decrease tumor stem cell growth, promote cell differentiation, disrupt tumor angiogenesis, and prevent tumor development[9]. Ibrutinib (pci-32765) is an irreversible inhibitor with high selectivity for bruton tyrosine kinase (BTK) and high potency, and Ibrutinib plus gemcitabine considerably improved survival rate in pre-clinical trials on pancreatic cancer[10-11]. In an Ib study evaluates the safety and tolerability

of pegvorhyaluronidase alfa （PEGPH 20） in combination with gemcitabine for advanced pancreatic cancer. Having been indicated by the results, PEGPH 20 was well tolerated, especially in patients with high hyaluronic acid[12]. It has also been found that adding istiratumab to gemcitabine and nab-paclitaxel improves chemotherapeutic activity[13]. Several studies demonstrated the high activity of hydroxychloroquine（HCQ）in pancreatic cancer model experiments, and HCQ can improve the efficacy of chemotherapy especially for pancreatic cancer[14,15]. As a heat shock protein antagonist, only by binding to heat shock protein 27（Hsp27）RNA, Apatorsen could function and will not be transformed into a functional protein, which can provide a new therapeutic idea for treating pancreatic cancer[16]. Low molecular weight heparin reduces the degradation of heparan sulfate proteoglycans by down-regulating the expression of heparinase[17,18]. In preliminary experiments, necuparanib has been found to inhibit tumor cell proliferation and invasion[19]. As a multi-targeted heparan sulfate mimetic, it effectively avoids the drawbacks of heparin analogs that are prone to bleeding while retaining anti-angiogenic effects[20,21], and it effectively participates in the anti-tumor immunomodulatory process[22]. In this paper, we conducted a more systematic collection and screening to evaluate the evidence and results of studies in relevant randomized controlled trials.

MATERIALS AND METHODS

Literature Search

With a combination method of computerized and manual, overall search was made by using key searching words “pancreatic cancer”, “gemcitabine”, “nab-paclitaxel” and “metastatic” for obtaining data in this paper. Having finished the last searching on 1 December, 2021, we only attached papers written in English.

Inclusion and exclusion criteria

Inclusion criteria: (1) The study met the requirements of the randomized control trials (RCTs) experimental design; (2) The trial group in the study was GA + a targeted drug

and the control group was GA regimen or GA + placebo; (3) The study subjects were patients with advanced or metastatic pancreatic cancer diagnosed by pathology; and (4) Observed indicators included OS, PFS, objective response rate (ORR) and toxicity rate (fatigue, anemia, diarrhea, vomiting, neutropenia).

Exclusion criteria: (1) Studies in patients with pancreatic cancer with significant comorbidities; (2) No complete observational index or single-arm pilot study; (3) Non-RCT studies such as observational, review, case report, and replication studies; and (4) Non-English studies.

Data extraction and quality evaluation

The titles and abstracts of all papers were evaluated by two investigators independently. If one of the investigators thought that the title and abstract of a particular paper had met the inclusion requirements; and the final decision was made by the two investigators after reading the full text together. Any conflicts during the screening process would be resolved through discussion or a third party. The methodological quality of the included studies was determined using the Jadad scale[23]. We only included high-quality studies. All data including first author, year of publication, number of patients in the trial and control groups, treatment regimen observations (overall survival, progression-free survival, objective response rate, and toxic response), and HR and 95% confidence interval in the survival curves should be extracted from the included studies.

Data analysis

Statistical analysis of all data in this paper was performed by Stata 15.1[24] and OS as the primary analysis; with PFS, ORR and adverse events as secondary analysis. Heterogeneity analysis before each trial was evaluated by Cochrane's Q test and I^2 statistics, and a random-effects model was used if $P > 0.1$ or $I^2 > 50\%$ indicated heterogeneity between studies[25]. In contrast, we used a fixed-effects model. The studies were evaluated for publication bias by funnel plot and Egger test. If P-value less than 0.05 indicates a statistical difference.

RESULTS

Literature search and research characteristics

The steps for evaluating the inclusion and exclusion of studies in this system are shown in the flow chart (Figure 1). In the process of searching, a total of 1886 relevant studies had been screened out as ineligible after the titles and abstracts (included duplicates, single-arm studies, meta-analyses, reviews, case reports, retrospective studies, control groups and experimental groups) being read and recognized as unqualified for the requirements. Had reading the full text, we excluded 13 RCT studies due to incomplete data and non-compliance of observation indicators; and we only included 7 RCTs[26-32] in the final meta-analysis. The main characteristics of the seven included RCTs are listed in Table 1, with a total of 1544 patients enrolled, including 853 patients in the GA+ a targeted drug group (tarextumab, Ibrutinib, PEGPH 20, istiratumab, apatorsen, HCQ and necuparanib) and 691 patients in the GA+ placebo group. All included trials met strict RCT trial design requirements and were of high quality (Jadad score >3.) Seven studies provided data on OS, ORR, and grade 3/4 toxicities (fatigue, anemia, diarrhea, vomiting and neutropenia).

OS meta-analysis

Median overall survival was provided for all 7 trials, and HRs and 95% confidence intervals for both are also available in the studies (Figure 2). Overall survival $I^2 = 0.0\%$, $P = 0.083$ was not heterogeneous, therefore we conducted a meta-analysis using a fixed-effects model. In accordance with the meta-analysis result, there was no marked difference between GA+ a targeted drug and GA+ placebo for improving OS (HR: 1.13, 95%CI: 1.00-1.27, $P = 0.044$).

PFS meta-analysis

Six trials provided median progression-free survival ($I^2 = 65.2\%$, $P = 0.013$), so we adopted a random-effects model (Figure 3). In line with the results, there was no marked

difference between GA+ a targeted drug and GA+ placebo for improving PFS (HR: 1.16, 95%CI: 0.93-1.43, *P* = 0.187).

ORR meta-analysis

Seven trials provided objective response rates, with objective response rate I^2 = 46.2%, *P* = 0.084, thus we used a dichotomous fixed-effects model for analysis (Figure 4). Based on the results, there was no significant difference in objective response rate between GA+ a targeted drug and GA+ placebo (0R: 0.99, 95%CI: 0.80-1.21, *P* = 0.892).

Tolerability

For grade 3/4 toxic reactions including fatigue, anemia, diarrhea, vomiting, and neutropenia were analyzed using a fixed-effects model (Table 2). As indicated by the results of the analysis, there was no significant difference between the two groups in fatigue (OR: 1.07, 95%CI: 0.88-1.29, *P* = 0.522), anemia (OR =0.97, 95%CI: 0.75-1.25, *P* = 0.822), vomiting (OR =1.07, 95%CI: 0.84-1.36, *P* = 0.595), neutropenia (OR =0.94, 95%CI: 0.73-1.22, *P* = 0.657), while there was a significant difference between the two groups in diarrhea (OR =1.46, 95%CI: 1.17-1.83, *P* = 0.001) (Figure 5).

DISCUSSION

Although GA regimen and modified FOLFIRINOX are the core first-line chemotherapy regimens for treating pancreatic cancer in clinical practice, we have to face the problem that the current chemotherapy regimens have restricted effect on prolonging the survival years of pancreatic cancer patients, and we need to keep attempting new approaches for fighting with pancreatic cancer. Having demonstrated the effectiveness of some new targeted drugs for anti-tumor therapy, clinical trials have started to use GA in combination with targeted drugs for pancreatic cancer. However, GA regimens combined with targeted drugs did not bring better efficacy and did not significantly improve OS, PFS and ORR. Moreover, even combination regimens were less effective than GA regimens. There was no difference in grade 3/4 toxicities including fatigue,

anemia, vomiting, and neutropenia in the toxicity evaluation, except for a significant increase in the incidence of diarrhea. The results of this systematic evaluation have important clinical implications, and more caution is needed for combining targeted agents on top of GA regimens in patients with metastatic pancreatic cancer.

The Notch pathway plays an important role in cancer treatment as anti-Notch 2/3 can reduce the incidence of tumors by downregulating Notch target genes. It has been found that anti-Notch 2/3 combined with chemotherapy is effective in a variety of cancers including pancreatic cancer, and it has been demonstrated that gemcitabine combined with anti-Notch 2/3 is more sensitive in the treatment of pancreatic cancer patients with a higher expression level Notch 3 gene[33]. It has also been shown that GA in combination with anti-Notch 2/3 drugs has stronger anti-tumor effects than gemcitabine alone[34]. Although tarextumab showed high potential in preclinical studies, the three low, medium and high Notch subgroups did not show any discrepancies in PFS, OS in a randomized phase II study[35]. The above result may be due to patient variation in clinical studies, whereas it also suggests that the specific role of the Notch pathway in pancreatic cancer is still controversial and needs further studies. Studies reported that BTK can be involved in a variety of immune-related signaling pathways, and it may be a new anti-tumor target[36]. Studies have shown that the combination of Ibrutinib and chemotherapy in the treatment of other cancers is beneficial in improving the effectiveness[37,38]. However, Ibrutinib did not improve PFS and OS in patients with metastatic pancreatic cancer in the phase III RESOLVE study[39], which was considered to be related to the addition of Ibrutinib shortening the treatment duration of the original GA regimen. The main component of the extracellular matrix is HA, increasing the interstitial gel fluid pressure within the tumor and reducing drug delivery to malignant cells. PEGPH 20 is a new drug degrading HA to increase cytotoxic release, and PEGPH 20 inhibits tumor growth by degrading the HA-assembled extracellular skeleton to disintegrate this matrix and thereby inhibit tumor growth[40]. Nevertheless, in a randomized trial of PEGPH 20 and modified FOLFIRINOX regimens for metastatic pancreatic cancer the primary endpoint of early termination of the PEGPH 20 and

modified FOLFIRINOX regimens median OS (7 mo *vs* 14.4 mo) has not been met[41]. Furthermore, the same occurred in a randomized controlled trial of PEGPH 20 and GA regimens, with a median OS of 11.2 mo for GA+ PEGPH 20 median OS of 11.6 mo for GA+ placebo (HR: 1.00, 95%CI: 0.80-1.27)[42]. Insulin-like growth factor receptor 1 (IGF-1R) is involved in tumor progression of pancreatic cancer promoting cancer cell growth. istiratumab, a novel bispecific antibody, enhances drug sensitivity by blocking inhibition of AKT phosphorylation and promoting degradation of IGF-1R and receptor tyrosine protein kinase B3, thereby restoring paclitaxel and gemcitabine activity. In a randomized clinical trial, ganitumab, an IGF-1R antibody, was added to gemcitabine, resulting in a significant improvement in OS for pancreatic cancer patients[43]. Besides, the trial was terminated early in a subsequent phase III clinical study. In the included trial, GA combined with istiratumab did not observe an improvement in OS or even a shorter PFS in the GA combined with istiratumab group even in the subgroup with high IGF-1R levels. There are many reasons for this result, among which may be related to the fact that blocking IGF-1R leads to a negative impact on the disease by compensatory signals from other pathways[44]. Cellular autophagy is closely related to the growth of cancer cells, and HCQ plays an effective role in inhibiting autophagy by inhibiting the binding of autophagosomes and lysosomes[45]. In a randomized study of colorectal cancer, the addition of HCQ to a regimen of FOLFOX (oxaliplatin, calcium folinate and fluorouracil) combined with bevacizumab did not significantly improve OS[46]. For this reason, it was expected that the addition of HCQ to GA would not improve OS. A retrospective analysis of the study revealed that the reason for this result may be due to genetic grouping imbalance but in-depth validation of the antitumor effect of HCQ is still needed. Hsp27 inhibits apoptosis by inhibiting caspase protein activity, and several malignancies, including pancreatic cancer, are highly expressed for Hsp27[47]. The activity of Apatorsen alone has been demonstrated in studies[48], and preclinical studies have demonstrated the role of Hsp27 in the treatment of pancreatic cancer[49]. However, in this paper including this GA regimen adding apatorsen, the apatorsen group had even worse performance

than the GA group. The above results indicated that any new targeted drug entering the clinic needs more rigorous trials and evaluation.

The mechanism of action of different targeted drugs for cancer treatment has its own complex characteristics. If the GA regimen is combined with targeted drugs of the same target, the results of the systematic analysis will definitely be more objective. However, there are insufficient data from studies on the combination of the same targeted drug with GA.

CONCLUSION

The GA regimen combined with targeted agents did not have promising results as in preclinical studies, the addition of novel targeted agents did not result in a survival benefit for patients with metastatic pancreatic cancer, and the targeted agents may bring more severe diarrheal toxic effects. Although the results are not optimistic, we expect more high-level clinical studies to be conducted to improve the evaluation of this system.

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ARTICLE HIGHLIGHTS

Research background

Pancreatic cancer is a highly malignant cancer. Gemcitabine plus albumin combined with paclitaxel (GA) is a common first-line treatment regimen for metastatic pancreatic cancer, and there is currently a great deal of clinical controversy about the effectiveness of adding a novel targeted agent to this regimen.

Research motivation

An analysis of studies using GA in combination with targeted drug regimens for the treatment of metastatic pancreatic cancer is presented to discuss its efficacy and safety.

Research objectives

Analysis comparing the effectiveness and safety of GA combined with targeted drug regimens and GA regimens.

Research methods

Eligible randomized controlled trials related to GA and GA+ targeted agents were first searched on PubMed, EMBASE and Cochrane, and then overall survival (OS), progression-free survival (PFS), objective response rates (ORR) and toxicity rates (TRs) were pooled and finally analyzed by Stata version 15.1.

Research results

The results showed no significant differences in PFS, OS, and ORR between GA+ targeted drugs and GA. Grade 3/4 TRs such as fatigue, anemia, vomiting, and neutropenia were not significantly different between the two groups, and the incidence of grade 3/4 diarrhea was significantly increased in GA+ targeted agents.

Research conclusions

Adding a novel targeted agent to the GA regimen did not improve survival in patients with metastatic pancreatic cancer.

Research perspectives

There is a gap between clinical and theoretical. Theoretically, new targeted drugs will improve the therapeutic effect but not the same result in the clinic.

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