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META-ANALYSIS

Meta-analysis of the Efficacy and Safety of Trastuzumab Combined with Apatinib in the Treatment of Advanced Gastric Cancer

Junzhong Yue, MM, Zhihua Long, MD

ABSTRACT

Objective • This study uses existing research results and literature to explore the effectiveness and safety of apatinib combined with trastuzumab in treating advanced gastric cancer. The goal is to establish a theoretical foundation for gastric cancer treatment and assist doctors in developing improved treatment plans.

Methods • Three databases were used in this study: the Cochrane Library, PubMed, and Embase. Keywords such as "gastric cancer," "trastuzumab," and "apatinib" were searched to screen and collect the data of the eligible studies. Data extraction and treatment evaluation were performed on the collected literature before conducting a meta-analysis.

Results • The combination of apatinib and trastuzumab showed promising results. The objective response rate, disease control rate, and median survival rate were significantly improved compared to trastuzumab alone. The treatment effect of apatinib combined with trastuzumab was found to be superior. However, it was noted that the incidence of hypertension was higher in the apatinib combined with the trastuzumab group. Furthermore, the levels of IFN-γ and TNF-α were higher in the combination group, while IL-10, IL-4, TSGF, CA199, and CEA levels were lower in the trastuzumab group. These findings suggest that apatinib combined with trastuzumab may offer better patient outcomes, although it is important to consider the potential adverse reactions associated with this combination therapy.

Conclusions • Current evidence shows that compared with trastuzumab, apatinib combined with trastuzumab has advantages in many aspects of treatment, and the therapeutic effect is more significant, which can effectively manage the disease progression in patients with gastric cancer, reduce the adverse reactions of patients to a certain extent, and improve the quality of life of patients. The sample size of this study was relatively small. Expanding the sample size will be necessary to obtain more accurate research results to enhance reliability and validity. (*Altern Ther Health Med.* 2024;30(6):70-75).

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INTRODUCTION

Many factors influence the occurrence of gastric cancer. The fast-paced lifestyle in modern society also causes many poor eating habits, such as irregular eating, fast eating, eating hard and dry food, and consuming hot drinks.[1,2] These eating habits can directly cause physical and chemical damage to the gastric mucosa, resulting in chronic gastritis.[3] Preserved food contains N-nitroso compounds (NOC) in small amounts compared with natural foods.[4] NOC is identified as a Class I carcinogen.[5] Contaminated food is also a risk factor for gastric cancer. Contaminated food contains a large amount of mycotoxin and N-nitrosamine compounds, which can cause inflammatory damage to the gastric mucosa and lead to precancerous changes in gastric mucosa.[6] Frequent consumption of fried and baked foods is another risk factor for gastric cancer.[7] These unhealthy foods not only lose their original nutritional value but promote the occurrence of gastric cancer similar to smoking, alcoholism, overeating, etc. Various biological effects, including inflammation inhibition, antioxidant activity, anti-proliferation, and angiogenesis can explain the protective factors of gastric cancer.[8]

Trastuzumab possesses inhibitory properties and can be used as an antitumor drug. Several studies examined the inhibitory effects of refrigerator use, education level, drinking coffee, and taking medications on gastric cancer.[9] Trastuzumab is an IgG1 antibody that is derived from human anti-HER2. It specifically targets HER2 cells, thereby inhibiting the activation of HER2 and its signaling pathways consequently suppressing tumor cell growth.[10] Clinical research has

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demonstrated that HER2 mutates or becomes overexpressed in 7-43% of patients.

Trastuzumab is the first molecular-targeted drug proven to benefit patients with advanced gastric cancer, significantly improving their survival rate.[11] Compared to the standard chemotherapy, overall survival rates were notably longer, with no observed increase in treatment-related adverse reactions.[12] Recent studies have introduced deruxtecan (DS-8201), a derivative of trastuzumab, which exhibits anti-tumor effects. It is an antibody-drug binding consisting of an anti-HER2 antibody, a degradable tetrapeptide connectome, and a cytotoxic topoisomerase I inhibitor.[13] Thus, the introduction of trastuzumab has significantly improved treatment strategies for patients with HER2-positive gastric cancer. This study, which focused on patients with advanced gastric and esophageal cancer, included 267 patients. Of these, 176 patients were assigned to receive second-line therapy, while the remaining 91 participants were administered a placebo. The investigation's findings revealed that the Planet Fourier spectrometer was utilized instead of the placebo group, resulting in a longer duration of treatment (2.6 months vs. 1.8 months). Moreover, the medium overall survival rate was significantly extended (6.5 vs. 4.7 months; $P = .0149$), indicating that patients experienced noticeable benefits while effectively managing any potential medication side effects.[14]

The U.S. FDA approved trastuzumab for the treatment of both breast cancer and gastric cancer that targets HER2. In 2010, a groundbreaking study named transoral gastroplasty (TOGA) unveiled the significant role of trastuzumab in the initial treatment of patients with HER2-positive gastric cancer. When combined with chemotherapy (either cismo combined with fluorouracil or variant regimen), trastuzumab demonstrated a considerable extension in the median survival of HER2-positive gastric cancer patients from 11.8 to 16 months.[15] At present, trastuzumab is the only targeted drug approved by National Comprehensive Cancer Network (NCCN) guidelines for the first-line treatment of unresectable gastric cancer. However, patients with HER2-positive gastric cancer often develop drug resistance to trastuzumab after approximately one year of treatment combined with chemotherapy.[16] Furthermore, while trastuzumab is effective across multiple lines of treatment for HER2-positive breast cancer, its efficacy in gastric cancer is limited to the first-line setting. This presents a critical challenge in managing HER2-positive advanced gastric cancer.[17]

The original concept behind antiangiogenic therapy was intended to destroy tumor blood vessels and deprive them of nutrients. However, it has been discovered that anti-angiogenic drugs do not "starve" tumors. High doses of these medications can aggravate the hypoxia and accumulation of metabolic waste in tumor tissues, ultimately promoting the growth and metastasis of tumor cells.[18] Harvard University professor Rakesh Jain first proposed the concept of vascular normalization. He observed that a low dose of antiangiogenic drugs caused the tumor's blood vessels to return to their normal state within a few days. However, a higher dose resulted in complete blockage of the tumor's blood supply.[19] Intratumoral circulation perfusion gradually improves with the tumor blood vessels returning to regular. This allows for better transportation and penetration of chemical drugs and immune cells into the tumor tissue. The improved hypoxic environment makes tumor cells more sensitive to physical radiation, increasing the effectiveness of chemotherapy, radiotherapy, and immunotherapy. Therefore, combining anti-angiogenic therapy with chemotherapy, radiotherapy, immunotherapy, and other treatments during the "tumor facular normalization" window can provide significant benefits. This approach enhances the delivery of therapeutic agents to the tumor site and improves the response rate to treatment.[20]

The inhibition of metalloproteinases effectively prevented the extracellular domain cleavage of HER2. In addition, it led to a decrease in VEGFR (vascular endothelial growth factor receptor) expression and inhibited angiogenesis. By reducing the binding of HER2 receptors to Src protein, the phosphorylation of PTEN tyrosine was inhibited, resulting in the activation of PTEN. Moreover, the induction of endocytosis of HER2 on the cell membrane surface led to a down-regulation of HER2 expression.[21] Numerous studies provide evidence for the clinical efficacy and controllable toxicity of combining apatinib with trastuzumab.[22,23] The aim is to identify clinical characteristic indicators related to treatment outcome and prognosis. This will enable the prediction of treatment efficacy of patients likely to benefit from the combination of apatinib and trastuzumab.

Given that many patients with advanced gastric cancer are elderly and often in poor health or have multiple underlying diseases, they may not tolerate combined chemotherapy (especially the combination of three drugs). Current domestic research has shown that the oral administration of apatinib combined with trastuzumab is an effective treatment for advanced gastric cancer. It offers definite efficacy while also having controllable adverse reactions. Therefore, this paper included several studies to evaluate systematically the effect of apatinib combined with trastuzumab in treating advanced gastric cancer and its influence on related cytokines.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

This study is a randomized controlled trial conducted and published domestically and internationally. The languages used are limited to Chinese and English.

The inclusion criteria of this study were: (1) Sample size was not fewer than 100 patients; (2) the study type was a case-control study; (3) the literature included in the reviewed materials required transparency or a calculable odds ratio (OR), and a 95% confidence interval (CI) for various factors affecting gastric cancer. The OR value was required to be the result of multi-factor logistics regression analysis; (4) the required quality score of included literature was ≥7 points; (5) the research objects were Chinese people; and (6) each study must be independent. If multiple literature sources

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have the same research subjects, the study with the largest sample size was selected.

Exclusion criteria for selecting literature for this study included: (1) literature with unknown publication dates; (2) literature with a sample size less than 100; (3) literature that repeated the same study with non-Chinese subjects or did not mention the subjects in the paper; and (4) literature with a quality score of fewer than 7 points. Literature reviews, systematic reviews, and case reports were also excluded, as well as literature with inconsistent intervention programs and outcome indicators. Finally, studies not randomized controlled trials (RCTs) were excluded from the analysis.

Search Strategy

To identify relevant studies, the researchers conducted a computer search using databases such as PubMed, Embase, Cochrane Library, CNKI (China National Knowledge Infrastructure), and Wanfang Data (until August 21, 2019). The search strategy combined subject headings and keyword retrieval in Chinese and English. For Chinese articles, the researchers used terms like "path for," "mesylate path for," "by bead sheet resistance," and "stomach cancer." In English, the keywords included: "apatinib," "S - 1," "gastric cancer," and "gastric carcinoma."

Literature Screening, Data Extraction, and Quality Evaluation

The minimum number of people engaged in the literature study was two. The process of selecting literature involved specific criteria, and when the author was concerned, a third-party researcher assisted in making decisions regarding the search. The data extraction indexes included various data such as general information (author, publication year, experimental population, age, etc.), experimental design (sample size, intervention group scheme), and outcome indicators (DCR [disease control rate], ORR [objective response rate], median PFS [progression-free survival], median OS [overall survival], adverse reactions, Th1, Th2, and related tumor markers). The Cochrane risk bias assessment tool in ReviewManager5.3 was employed to assess the quality.

Statistical Analysis

The researchers relied upon RevMan, a software for data analysis. When indexing literature data, the researchers employed the weighted average method. The effect index was utilized as a standard measure to address any unit disparities during the study. The research primarily focused on the median and non-disease survival periods of the subjects involved. A comparison was made between these two patient indicators, and the data was analyzed using the random effect model.

RESULTS

Literature Screening Results and Basic Information Included in the Study

One hundred seventy-eight articles were retrieved; 20 (Table 1[3-22]) were ultimately included based on the screening method outlined in Figure 1. As a result, this study included 1150 patients. The experimental group and control group were 576 and 574, respectively.

Figure 1. Literature Screening Process

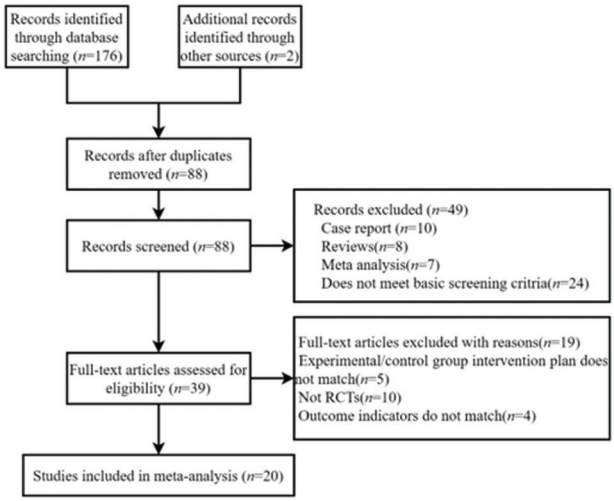

Table 1. Basic Features of the Included Literature

Author (years)	Age (years)	Object of study	Experimental / control group (n)	Interventing measure of experimental group	Outcome indicator
Bao Yu 2019[3]	>30	AGC	49 /48	Apatinib 500 ~ 850 mg + S-1	ABCDEHIJ
Chen Zhaojun 2019[4]	45-79	AGC	40/40	Apatinib 500 mg + S-1	ABCIJ
Lv Xiaoyan 2019[5]	49-78	AGC	23/23	Apatinib 250 ~ 500 mg + S-1	ABC
Ji Huaqing 2019[6]	38-78	AGC	20/20	Apatinib 500 mg + S-1	ABC
Wang Fang 2019[7]	60-83	First line and above AGC	29/29	Apatinib 500 mg + S-1	ABC
Yang Ningjuan 2019[8]	61-85	AGC	24/24	Apatinib 250 ~ 500 mg + S-1	ABCDF
Cai Hongxu 2018[9]	65-76	Second line AGC	40/40	Apatinib 250 ~ 500 mg + S-1	ABC
Ai Liang 2018[10]	47-78	Second line AGC	30/30	Apatinib 850 mg + S-1	ABCH
Xiong Yi 2018[11]	27-70	Second line and above AGC	32/32	Apatinib 850 mg + S-1	ABC
Huang Yichao 2018[12]	44-78	Second line AGC	15/15	Apatinib 500 ~ 850 mg + S-1	ABCDGHIJ
Zhou Lei 2018[13]	N	First line and above AGC	20/20	Apatinib 850 mg + S-1	ABCH
Wu Zhiwei 2017[14]	25-74	First line and above AGC	14/14	Apatinib 500 mg + S-1	ABC
Fan Xinxin 2017[15]	26-73	First line AGC	15/15	Apatinib 500 mg + S-1	ABC
Gao Jingping 2017[16]	47-83	First line and above AGC	16/15	Apatinib 500 ~ 850 mg + S-1	ABC
Li Dehua 2019[17]	50-78	First line AGC	26/26	Apatinib 500 mg + S-1	ABC
Gou Lanqiong 2019[18]	62-73	First line and above AGC	75/75	Apatinib 250 ~ 500 mg + S-1	ABC
Bai Xue 2018[19]	24-73	AGC	30/30	Apatinib 250 mg + S-1	ABC
Hu Shanshan 2016[20]	49-78	AGC	23/23	Apatinib 800 ~ 850 mg + S-1	ABC
Ou Zhangsong 2019[21]	46-79	AGC	24/34	Apatinib 500 mg + S-1	ABC
Jing Xiaohui 2016[22]	N	AGC	21/21	Apatinib 500 mg + S-1	ABC

Literature Quality Evaluation

The results suggest no bias risk in the studies included both experimental and control groups (Figure 2).

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Figure 2. Results of Bias Risk Assessment in Included Studies

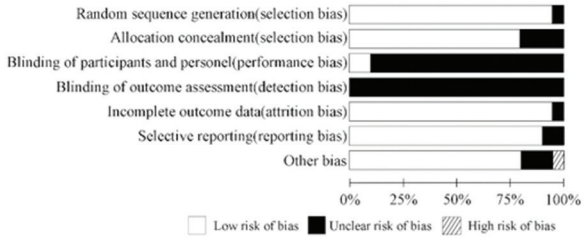

Figure 3. Meta-analysis of Median PFS in Two Groups of Patients

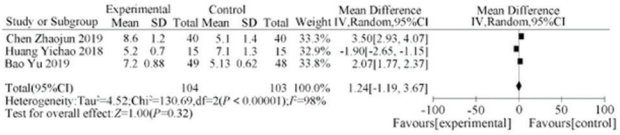

Figure 4. Meta-analysis of Median OS in Two Groups of Patients

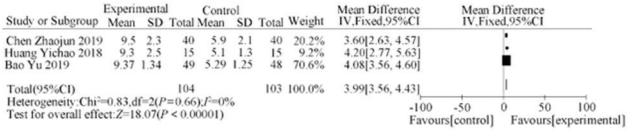

Table 2. Meta-analysis Results of the Incidence of Adverse Reactions in the Two Groups

Adverse reactions	Number of studies	Sample size (n)	OR	95% CI	*P* value
Nausea or vomit	16	911	0.85	[0.16, 1.16]	.30
Hepertension	11	565	6.19	[1.89, 20.23]	.003
Diarrhea	15	823	0.93	[0.62, 1.40]	.72
Hand - foot syndrome	14	798	1.35	[0.92, 1.98]	.13
Proteinuria	11	735	4.02	[1.11, 14.62]	.03
Myelosuppression	15	878	1.08	[0.72, 0.61]	.72
Liver injury	4	338	0.87	[0.31, 2.47]	.79
Mucositis	6	246	1.29	[0.69, 2.44	.42
Weakness	13	701	1.08	[0.75, 1.54]	.69
Neurotoxicity	6	396	1.15	[0.72, 1.84]	.55
Hemorrhage	3	276	1.52	[0.61, 3.76]	.37
Rash	2	230	0.75	[0.52, 5.90]	.37

Median PFS

There were relatively few studies on median PFS, and the results showed no significant difference in median progression-free survival between the apatinib combined with the trastuzumab and trastuzumab groups (Figure 3).

Median OS

There were relatively few studies on median OS, and the results showed that the median overall survival in the apatinib combined with the trastuzumab group was significantly higher than the trastuzumab group, with statistical significance (Figure 4).

Adverse Reactions

The incidence of hypertension and albuminuria in the apatinib combined trastuzumab group was significantly higher than that in the trastuzumab group, and no significant difference was observed in other adverse reactions (Table 2).

DISCUSSION

In China, about 403 000 people are newly diagnosed with stomach cancer every year.[24] Early gastric cancer can be cured, but most patients with gastric cancer are already locally advanced or have distant metastasis at the first diagnosis.[25] The hope is that breakthroughs can be found in targeted therapies or immunotherapy.

Antiangiogenic therapy is one targeted therapy strategy. The occurrence and development of tumors are closely related to the formation of neovascularization. Research suggests that tumors begin to have an independent blood supply when they grow more than 3 millimeters in diameter.[26] There are few effective anti-angiogenesis targeted drugs for advanced gastric cancer. Clinical trials of a new generation of antiangiogenic drugs, including anlotinib (NCT02461407), are ongoing, but no data has been released yet. Apatinib targets VEGFR-2, a small molecule TKI (Tyrosine Kinase Inhibitor) drug independently developed in China and targeted against angiogenesis.[27]

The landscape of cancer research is constantly evolving, and as a result, the circumstances faced by cancer patients are also changing. One notable change is the increase in the tumor volume observed in some patients. Clinical cancer treatment is continuously encountering new challenges and obstacles. The apatinib application has shown promising results in improving patient survival rates and other aspects of cancer therapy. However, it is essential to note that not all patients derive the desired therapeutic benefits using apatinib. Furthermore, accurately determining the scope of efficacy remains a challenge. Resistance to the drug, as well as other adverse reactions, have been reported in patients over a year or more. Studies investigating the combined use of apatinib with other treatments have demonstrated a certain degree of improvement in patient survival rates.[27] The drug resistance of trastuzumab in gastric cancer is more severe than its use in breast cancer. Unfortunately, a variety of novel antibodies that have proven effective in reversing trastuzumab resistance in breast cancer, such as lapatinib, pertuzumab, and T-DM1, have shown limited efficacy in gastric cancer.[28, 29]

VEGFR-2 is the specific target for apatinib. A breast cancer study indicated that individuals with high levels of VEGFR-2 expression achieved longer PFS and OS after apatinib treatment compared to those with low VEGFR-2 expression. Moreover, patients with adverse hypertensive events also had longer PFS and OS than those without elevated blood pressure.[30]

VEGFR-2 expression and adverse events may be predictive markers of the efficacy of apatinib in treating malignant tumors. The study of apatinib's impact on osteosarcoma lung metastasis has also reported similar findings.[31] However, some patients with high VEGFR-2 expression do not benefit, which may be related to the poor prognosis of the VEGFR-2 expression factor itself. Although there is no evidence supporting the predictive value of VEGFR-2 expression in gastric cancer patients, it is widely believed that the blood supply within the tumor itself plays a

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crucial role in determining the efficacy of antiangiogenic therapy. In fact, in xenograft tumor models of gastric cancer, tumors with a high microvascular density (indicated by high CD31 expression) have shown greater sensitivity to apatinib.[32]

Clinical case reports on gastric cancer have discovered that patients who benefited from apatinib had an amplification of VEGF-related genes. At present, no recognized tumor biomarker can accurately identify the population who will benefit from apatinib treatment for advanced gastric cancer. Apatinib down-regulates VEGFR2 protein expression in ovarian cancer cells. However, another study showed that apatinib did not affect the expression of the VEGFR2 protein in NSCLC (non-small cell lung cancer) cells. Instead, its main effect is blocking VEGFR2 phosphorylation and downstream signaling pathways. Some researchers have found that apatinib competitively inhibits the binding of VEGF and VEGFR2 in gastric cancer cells, thus blocking the auto-phosphorylation process of VEGFR2 and inhibiting tumor angiogenesis.[33]

There are some limitations to the reviewed studies. The inclusion and exclusion criteria and efficacy criteria were not uniformly adopted across all studies. Despite extensive searches, there remains a possibility of potential publication bias. Additionally, subgroup analysis based on ECOG scores and regional differences could not be performed due to limitations in the original data.

Additionally, the use of trastuzumab in the treatment of HER2-positive breast cancer has been shown to extend significantly both the patient's PFS and OS. When implementing this treatment approach in clinical practice, it is essential to have real-time monitoring in place. However, it should be noted that this study is based on previous research findings, and there may be some limitations due to the current state of research and lack of comprehensive examinations.

The results of this study provide a certain amount of data and treatment for gastric cancer.[34] However, it is essential to conduct further research with larger sample sizes and more reliable data to advance the treatment of gastric cancer. Despite ongoing studies on drug development, the progress in targeted treatments for gastric cancer lags behind that of breast cancer and colorectal cancer. Overall, the research in the field of gastric cancer remains at a relatively low level.[35]

The effectiveness of trastuzumab and apatinib in treating gastric cancer has been demonstrated and indicates their potential for disease control.[36] There are relatively few medications available for treating gastric cancer. However, more drugs and treatments are being applied in clinical medicine. Meanwhile, immunotherapy, such as immune checkpoint inhibitors, shows great promise.[37] Clinical studies have demonstrated significant survival benefits with chemotherapy (trifluridine/tipraxil, FLOT regimen), targeted therapy (apatinib, remurozumab, etc.), and immunotherapy (opdivo, pembrolizumab, etc.).[36-38] In the future, combining chemotherapy, targeted drugs, and immunotherapy in research studies may help to optimize survival outcomes.

ETHICAL COMPLIANCE

Not applicable.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

JY and ZL designed the study and performed the experiments, JY collected the data, ZL analyzed the data, JY and ZL prepared the manuscript. All authors read and approved the final manuscript. JY and ZL contributed equally to this work.

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