Original Article
Clinical study on the safety, efficacy, and prognosis of molecular targeted drug therapy for advanced gastric cancer

Liang Wang[1], Wei Li[1], Yagang Liu[1], Cui Zhang[1], Weina Gao[2], Lifei Gao[3]

[1]*The Second Department of General Surgery,* [2]*The fourth Department of Endocrinology,* [3]*The Third Department of General Surgery, Cangzhou Central Hospital, Cangzhou, Hebei Province, China*

Abstract: Objective: To investigate the safety, efficacy, and prognosis of advanced gastric cancer patients treated with molecular targeted drug therapy. Methods: A total of 200 patients with metastatic gastric cancer admitted to our hospital from March 2018 to December 2018 were randomly selected and divided into the control group, group A, group B and group C, with 50 patients in each group. Patients in the control group received surgical treatment combined with conventional chemotherapy. Patients in group A were provided with surgical treatment combined with bevacizumab, patients in group B received surgical treatment combined with apatinib, and patients in group C received surgical treatment combined with recombinant human endostatin (RHE). Clinical efficacy, vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor 2 (VEGFR-2) levels, Response Evaluation Criteria in Solid Tumors (RECIST), sentinel lymph node (SLD) metastasis, and adverse reactions were compared among different groups of patients with metastatic gastric cancer. Results: There were no significant differences in treatment efficiency, VEGF and VEGFR-2 levels, RECIST, SLD metastasis value and adverse reactions among group A, group B and group C, and the results were not statistically significant ($P > 0.05$). The levels of VEGF, VEGFR-2, SLD metastasis, and adverse reactions in group A, B, and C were significantly lower than those in the control group ($P < 0.05$). The effective rate of treatment and RECIST in group A, B and C were significantly higher than those in the control group, and the comparison results were statistically significant ($P < 0.05$). Conclusion: Molecular targeted drug therapy is effective and safe in patients with advanced gastric cancer, and the prognosis of patients is satisfactory, without the proliferation and metastasis of cancer cells.

Keywords: Molecular-targeted drugs, advanced gastric cancer, security, effectiveness, the prognosis of outcome

Introduction

Gastric cancer currently ranks top in cancer-related mortalities worldwide, and patients with it always have a somber prognosis [1-3]. Currently, tumor resection, radiotherapy, and chemotherapy are the mainstay of treatment. However, it is most often diagnosed at an advanced stage, after becoming metastatic at distant sites [4-6]. Therefore, early screening of biological indicators for tumor metastasis is necessary. Studies have shown that VEGF and VEGFR-2 levels can serve as indicators to predict whether the tumor will have lymphatic metastasis [5, 6]. Targeted therapy is a type of therapy that customizes the usage of medication based on patients' individual conditions.

Molecular targeted drug therapy is relatively common in treating malignant tumors in current medical research; it mainly focuses on molecular targeted drug's mechanism and clinical effects on treating malignant tumors. Relevant study states that molecular targeted drug therapy is superior to routine radiotherapy and chemotherapy in treating malignant tumors, because it remarkably extends patients' survival time and improves the cure rate from gastric cancer [7-9]. Response Evaluation Criteria in Solid Tumors (RECIST) emphasizes that tumor markers are expected to reach the normal level in addition to the complete disappearance of the tumor stipulated by the criteria for clinical recovery. Additionally, the RECIST 1.1 version issued new criteria on the progress and

the clinical stability. The new regulations have further expanded the clinical stability criteria for some tumors, suggesting the importance of survival with tumors, and making the efficacy evaluation more accurate by calculating the number of people with SLD metastasis. The primary aim of the present study was to investigate the safety, efficacy, and prognosis of molecular targeted drug therapy in advanced gastric cancer.

Materials and methods

General materials

A total of 200 patients with metastatic gastric cancer admitted to our hospital from March 2018 to December 2018 were randomly selected and divided into the control group, group A, group B and group C, with 50 patients in each group. The control group included 23 males and 27 females with an average age of (56.75±2.54) years old and an average disease course of (1.05±0.34) years. There were 6 cases of hypertension, 7 cases of diabetes, and 3 cases of hyperlipidemia. Group A included 25 males and 25 females with an average age of (57.51±2.01) years old and an average disease course of (1.13±0.19) years. There were 5 cases of hypertension, 7 cases of diabetes, and 5 cases of hyperlipidemia. Group B included 24 males and 26 females with an average age of (55.29±3.99) years old and an average disease course of (1.25±0.28) years. There were 6 cases of hypertension, 8 cases of diabetes, and 2 cases of hyperlipidemia. Group C included 26 males and 24 females with an average age of (56.88±2.54) years old and an average disease course of (1.35±0.31) years. There were 8 cases of hypertension, 8 cases of diabetes, and 1 cases of hyperlipidemia. There were no significant differences among the four groups' general information (P>0.05).

Inclusion/exclusion criteria

Inclusion criteria

① Patients who met the clinical manifestation of advanced gastric cancer. ② Patients aged 40 to 60 years old. ③ No other malignant tumors and with normal cardio, pulmonary, and renal function. ④ No major surgeries recently. ⑤ Patients participated in this research voluntarily and signed the informed consent form.

This study obtained approval from our hospital's research ethics committee.

Exclusion criteria

① Patients with incomplete liver function. ② Patients with cognitive disorder, unconsciousness or mental disorder. ③ Patients with allergies or were allergic to related medicines. ④ Patients with autoimmune diseases.

Methods

The margin was required to be negative for surgical treatment of advanced gastric cancer in 4 groups (control group, group A, B, C). Surgical resection methods include subtotal gastrectomy and total gastrectomy; for distal gastric cancer, subtotal gastric resection is preferred. The surgical method of proximal gastric cancer is based on the actual situation of the patient, and proximal gastrectomy or subtotal gastrectomy is selected. Conventional chemotherapy treatments include mitomycin or cisplatin as basic chemotherapy drugs. The control group had surgery combined with conventional chemotherapy. Group A received surgery combined with bevacizumab (manufacturer: Roche Pharma (Switzerland) Ltd, batch number: S20120069, specification: 400 ml/bottle) for treatment, intravenous injection, 5 mg/kg, once two weeks. Group B was provided surgery combined with apatinib (manufacturer: Jiangsu Hengrui Medical Corp., Ltd, SFDA approval number: H20140103, specification: 850 mg) for treatment, 2 pills per time, once a day, per os. Group C received surgery combined with RHE (manufacturer: Shandong Xiansheng Maidejin Bio Pharmaceutical Ltd, SFDA approval number: S20050088, specification: 15 mg/$2.4×10^5$ U/3 ml/bottle) for treatment, intravenous injection, dissolve $1.2×10^5$ U/m^2 in 250 ml 0.9% sodium chloride injection, intravenous drip at constant speed for 3 h, keep using RHE for 14 days, stop for a week and continue delivering for 14 days. After two weeks of treatment, 3 ml fasting venous blood was collected, centrifuged at 3000 r/min for 10 min, and the supernatant was collected to test serum's VEGF and VEGFR-2 levels.

Observation indexes

The treatment efficacy, VEGF and VEGFR-2 levels, RECIST, SLD metastasis value and adverse
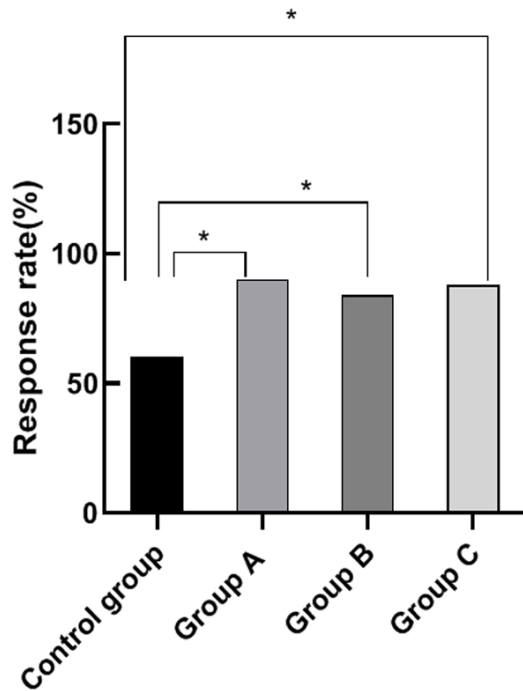
Figure 1. Comparison of treatment efficiency. Note: The horizontal axis stands for the groups, and the vertical axis stands for treatment efficiency. From left to right, the treatment efficiency of the four groups respectively is 60%, 90%, 84%, and 88%. a, comparison between the control group and group A (x^2=12.00, P=0.001) (P<0.05). b, comparison between the control group and the group B, (x^2=7.14, P=0.008) (P<0.05). c, comparison between the control group and the group C, (x^2=10.19, P=0.001) (P<0.05).

reactions among different groups were compared. Excellent means the target lesions basically disappeared. Effective means no increase in target lesions. Ineffective means there is an increase in target lesions. The lower the VEGF and VEGFR-2 levels are, the higher patients' survival rate is.

Complete remission (CR): all the target lesions disappear; partial remission (PR): the sum of maximum diameters reduce by at least 30%; progressive disease (PD): the sum of maximum diameters reduce by at least 20% or new lesions appear; stable disease (SD): there are certain reduction in the sum of maximum diameters, but the reduction fails to reach PR; or there are certain increase in the sum of maximum diameters, but the increase fails to reach PD [10-12]. Objective remission rate (ORR)= CR+PR, disease control rat (DCR)=CR+PR+SD.

The modified Clavien-Dindo classification system was applied to evaluate the adverse reactions after treatment. Level 0: no complications occur after surgery. Level 1: complications don't need drug intervention. Level 2: complications need drug intervention. Level 3 complications need other interventions besides drug intervention. Level 4: complications are life-threatening. Level 5: complications result in death.

Statistical analysis

Statistical analysis was performed using the SPSS statistical software 20.0. The measurement data were represented by ($\overline{x} \pm sd$). For inter-group comparisons, data were analyzed with LSD-t test. For multiple-group comparisons, data were analyzed with one-way analysis of variance or repeated measures analysis of variance (RMANOVA). The enumeration data were examined by χ^2 and represented by [% (n)]. And *P<0.05* was considered as statistically significant.

Results

Comparison of the treatment efficiency

For the control group, there were 15 excellent cases, 15 effective cases, and 20 ineffective cases. For group A, there were 26 excellent cases, 19 effective cases, and 5 ineffective cases. For group B, there were 25 excellent cases, 17 effective cases, and 8 ineffective cases. For group C, there were 22 excellent cases, 22 effective cases, and 6 ineffective cases. There were no significant differences among the treatment efficiency of group A, B and C (P>0.05). The treatment efficiency of group A, B and C were significantly greater than that of the control group (P<0.05). See **Figure 1**.

Comparison of VEGF, VEGFR-2 levels

There were no significant differences among the VEGF and VEGFR-2 levels of group A, B and C (P>0.05). The VEGF and VEGFR-2 levels of group A, B and C were significantly lower than those of the control group (P<0.05), indicating a higher survival rate for patients. This result demonstrates that molecular targeted drug therapy can effectively increase the survival
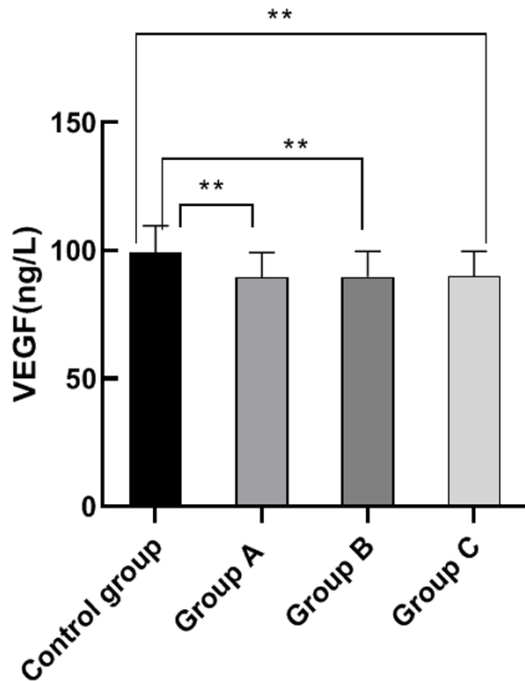
Figure 2. Comparison of VEG level. Note: The horizontal axis stands for the groups, and the vertical axis stands for VEGF level. From left to right, the VEGF level of the four groups respectively is (99.28±10.35) ng/L, (89.52±9.66) ng/L, (89.69±10.02) ng/L, and (90.00±9.68) ng/L. a, comparison between the control group and the group A, (t=4.87, P<0.001) (P<0.05). b, comparison between the control group and the group B, (t=4.71, P<0.001) (P<0.05). c, comparison between the control group and the group C, (t=4.63, P<0.001) (P<0.05).
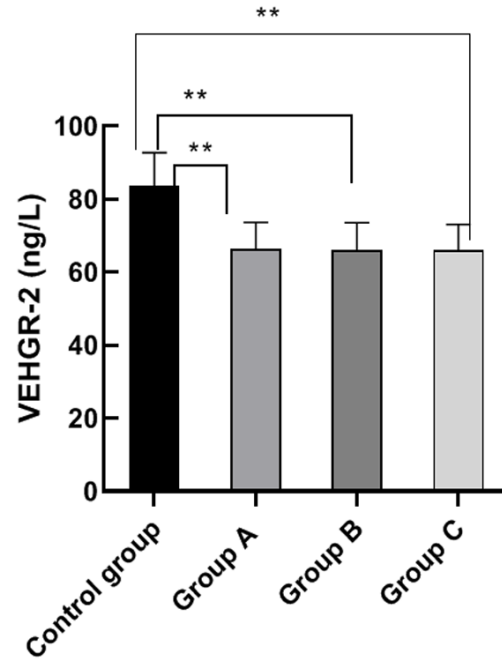

Figure 3. VEGFR-2 levels. Note: The horizontal axis stands for the groups, and the vertical axis stands for VEGFR-2 level. From left to right, the VEGFR-2 level of the four groups respectively is (83.50±9.21) ng/L, (66.35±7.24) ng/L, (65.98±7.54) ng/L, (66.08±7.00) ng/L. a, comparison between the control group and the group A (t=10.35, P<0.001) (P<0.05). b, comparison between the control group and the group B (t=10.41, P<0.001) (P<0.05). c, comparison between the control group and the group C (t=10.65, P<0.001) (P<0.05).

rate for patients with advanced gastric cancer. See **Figures 2** and **3**.

Comparison of RECIST standards

There were no significant differences among the RECIST standards' ORR and DCR of group A, B and C (P>0.05). The RECIST standards' ORR and DCR of group A, B and C were significantly higher than those of the control group (P<0.05). This comparison shows that molecular targeted drug therapy can effectively improve the clinical effects and prolong the survival time for patients with advanced gastric cancer. See **Figure 4**.

Comparison of SLD metastasis value

Control group's SLD metastasis value was significantly high than that of group A, B and C (P<0.05). There were no significant differences among the SLD metastasis value of group A, B and C (P>0.05). This result proves that molecu-

lar targeted drug therapy can effectively inhibit the metastasis of cancer cells for patients with advanced gastric cancer. See **Figure 5**.

Comparison of adverse reactions rate

During treatment, all the groups exhibited neutropenia, nausea, vomiting, and rash. The adverse reactions rate of the control group was significantly higher than that of group A, B and C (P<0.05). There were no significant differences among the adverse reactions rate of group A, B and C (P>0.05). This comparison reveals that molecular targeted drug therapy results in high safety and has a better prognosis for patients with advanced gastric cancer. See **Figure 6**.

Discussion

Molecular targeted drug therapy has been attracting a great deal of attention in the context of malignant tumors [13-15]. According to
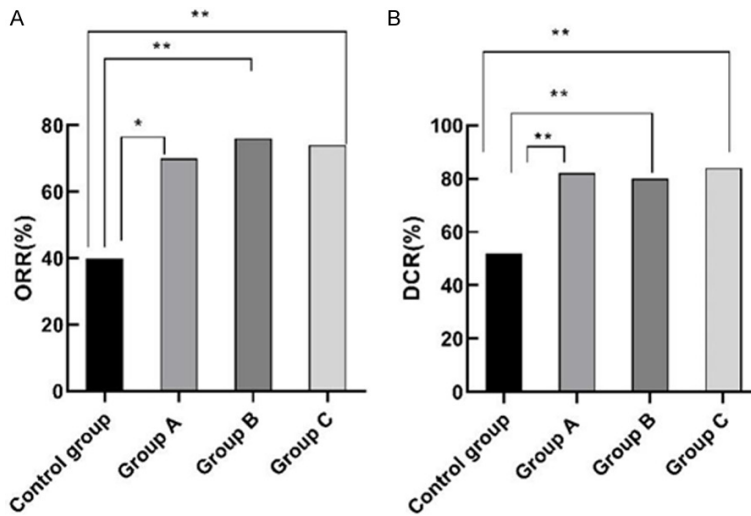
Figure 4. Comparison of RECIST standards. Note: For (A), the horizontal axis stands for the groups, and the vertical axis stands for ORR. From left to right, the ORR of the four groups respectively is 40%, 70%, 76%, 74%. a, comparison between the control group and the group A (x^2=9.09, P=0.003) (P<0.05). b, comparison between the control group and the group B x^2=26.60, P<0.001 (P<0.05). c, comparison between the control group and the group C (x^2=23.58, P<0.001) (P<0.05). For (B), the horizontal axis stands for the groups, and the vertical axis stands for DCR. From left to right, the DCR in the four groups respectively is 52%, 82%, 80%, 84%. a , comparison between the control group and the group A (x^2=20.35, P<0.001) (P<0.05). b, comparison between the control group and the group B (x^2=17.47, P<0.001) (P<0.05). c, comparison of control group and group C (x^2=23.53, P<0.001) (P<0.05).

drugs, including apatinib, bevacizumab and RHE, in advanced gastric cancer. Apatinib is a small-molecule targeted anti-VEGFR-2 drug for advanced gastric cancer patients who have failed second-line chemotherapy. It blocks downstream signal transduction and inhibits the formation of tyrosine kinase through highly selective competition for the ATP binding site of intracellular receptor-2, thereby inhibiting the formation of new blood vessels in tumor tissues, and ultimately achieves the purpose of treating tumors [23]. Additionally, Bevacizumab is a recombinant human monoclonal IgG1 antibody that acts by inhibiting the biological activity of human vascular endothelial growth factor. In other words, Bevacizumab can bind to VEGF and prevent it from binding to receptors on the surface of endothelial cells. In an in vitro angiogenesis model, the binding of VEGF to its corresponding receptor can lead to endothelial cell proliferation and angiogenesis [24]. Furthermore, RHE can inhibit the expression of vascular endothelial growth factor and can inhibit tumor growth. Vascular endothelial growth factor is a cytokine that promotes the growth of blood vessels. It plays a role in the occurrence and development of tumors and other tissues. Therefore, targeted inhibition of the expression of vascular endothelial growth factor can inhibit the occurrence and development of tumors and other diseases [25].

related research, the application of apatinib in advanced gastric cancer has garnered a remarkable outcome. Through oral administration of apatinib, patients' symptoms can be improved, and the deterioration can be postponed [16-18]. Additionally, prior research has stated that the application of bevacizumab and RHE has better clinical effects and better safety regarding treating malignant tumors. Gastric cancer is a malignant tumor with high mortality rate and morbidity rate. Patients with advanced gastric cancer suffer from great pain, and the adverse reactions owing to tumor resection easily lead to recurrence, proliferation, and metastasis. Moreover, radiotherapy and chemotherapy, if adopted, not only have low efficiency, but also have strong negative influence on patients' health, triggering oral disease, retinal diseases, skin diseases, etc. [19-22]. Therefore, molecular targeted drug therapy is a great topic in the treatment of patients with advanced gastric cancer.

This study aims at investigating the safety, efficacy, and prognosis of molecular targeted

The results of the present study show that the treatment efficiency of groups treated with molecular targeted drugs was significantly higher than that of the control group (P<0.05). The VEGF and VEGFR-2 levels of groups treated with molecular targeted drugs was significantly lower than that of the control group (P<0.05). The lower the VEGF and VEGFR-2 levels, the higher the patients' survival odds. Thus, molecular targeted drug therapy can obviously increase the survival rate for patients with
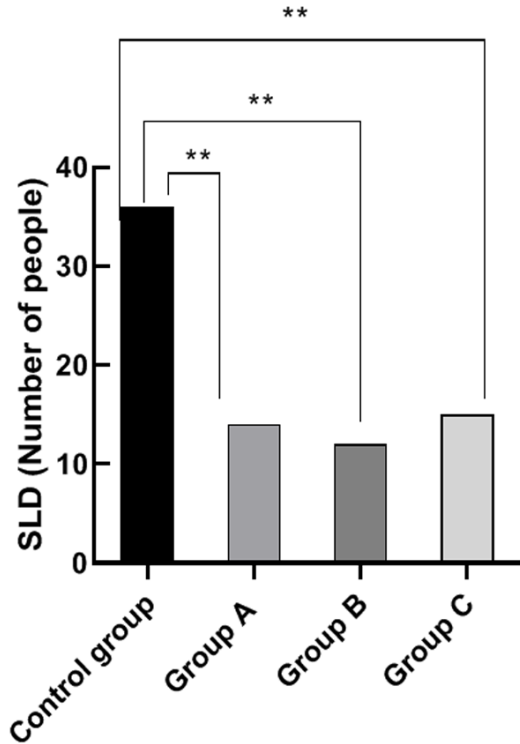
Figure 5. Comparison of SLD metastasis value. Note: The horizontal axis stands for the groups, and the vertical axis stands for SLD metastasis value. From left to right, the SLD metastasis in the four groups respectively is 36 cases, 14 cases, 12 cases and 15 cases. a, comparison between the control group and the group A (x^2=19.36, P<0.001) (P<0.05). b, comparison of control group and group B (x^2=23.08, P<0.001) (P<0.05). c, comparison between the control group and group C (x^2=17.65, P<0.001) (P<0.05).
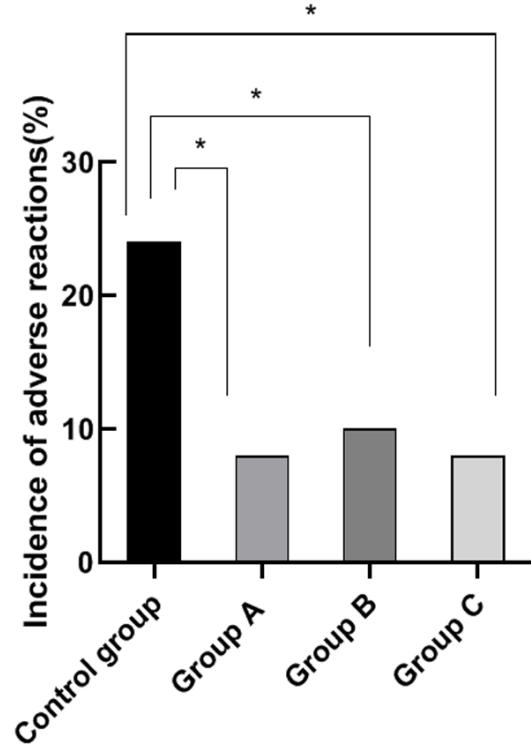

Figure 6. Comparison of adverse reactions rate. Note: The horizontal axis stands for the groups, and the vertical axis stands for adverse reactions rate. From left to right, the adverse reactions rate of the four groups respectively are 24%, 8%, 10%, 8%. a, comparison between the control group and the group A (x^2=9.52, P=0.002) (P<0.05). b, comparison between the control group and the group B (x^2=6.95, P=0.008) (P<0.05). c, comparison between the control group and group C (x^2=9.52, P=0.002) (P<0.05).

advanced gastric cancer. We also found that the ORR and DCR of the control group were obviously lower than those of groups treated with molecular targeted drugs (P<0.05). Furthermore, the smaller the SLD metastasis value is, the less patients' metastatic cancer cells are, and the better patients' conditions are. We observed that the SLD metastasis value of the control group was significantly higher than that of groups treated with molecular targeted drugs (P<0.05), which shows that molecular targeted drug therapy can effectively control the conditions and reduce the odds of cancer cells metastasis.

A prior trial proposed that [26] apatinib can obviously inhibit VEGFR-2 level, wherein the mouse xenografts transplantation model, apatinib strongly inhibit the growth of cell CT26 by inhibiting catenin signaling pathways and angiogenesis, hence achieving the result of

treating rectal cancer with targeted therapy. This result resonates with our result that patients treated with molecular targeted drug therapy has lower VEGFR-2 level. The limitation of this study is that the long-term follow-up is not conducted, and the long-term disease-free survival time cannot be thus calculated. In the future, long-term follow-up trials are needed to provide guidance for advanced gastric cancer treatment.

In conclusion, molecular targeted drug, including apatinib, bevacizumab and RHE, is a preferred method for patients with advanced gastric cancer in terms of high efficacy and safety. Importantly, the prognosis outcome is satisfactory without proliferation and metastasis.

Disclosure of conflict of interest

None.

Address correspondence to: Lifei Gao, The Third Department of General Surgery, Cangzhou Central Hospital, Cangzhou, Hebei Province, China. Tel: +86-15100375646; E-mail: Lifei_Gao@126.com

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