

Study on the clinical effects of targeted therapy on elderly patients with gastric cancer

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Abstract: To explore the clinical effects of targeted drug therapy on elderly patients with gastric cancer. Totally 200 metastatic gastric cancer patients who came to our hospital from January 2017 to January 2020 were selected and randomized into four groups, with 50 patients in each group. Bevacizumab (Group I), apatinib (Group II), and recombinant human endostatin (Group III) adopted respectively. While the control group received no targeted drug. Clinical data and clinical effect was collected and compared. After the therapy, the vascular endothelial growth factor (VEGF), soluble vascular endothelial growth factor receptor-2 (sVEGFR2) and human epithelial growth factor receptor-2 (HER2) positive detection of Group I, Group II, and Group III were better than the control group ($P < 0.05$). In addition, the therapeutic effects of Group I, Group II, and Group III were higher and the incidence of adverse reactions was lower than the control group ($P < 0.05$). Targeted drugs have obvious clinical effects in gastric cancer. It can effectively inhibit tumor growth and reduce the occurrence of complications, which is worthy of extensive clinical application and promotion.

Keywords: Gastric cancer, targeted drugs, bevacizumab, apatinib, recombinant human endostatin.

INTRODUCTION

Gastric cancer is one of the most common malignant tumors in the world, yet the incidence and mortality of gastric cancer in China ranks third among all malignant tumors, which is a serious health hazard to people (Guggenheim *et al.*, 2013; Song *et al.*, 2017). For advanced gastric cancer, chemotherapy is basically the main clinical therapy. However, the complete remission rate of present chemotherapy is low, and the duration of remission is quite short even if the remission is achieved after the chemotherapy (Choi *et al.*, 2015). In recent years, with the in-depth study of the technology of tumor molecular biology, molecular-targeted drugs have been showing a significant anti-tumor activity (Pellino *et al.*, 2019). Bevacizumab is a recombinant humanized monoclonal antibody that binds to VEGF. It can bind to VEGF and prevent its interaction with vascular endothelial growth factor receptor, to play an anti-angiogenesis role and inhibit tumor growth (Ohtsu *et al.*, 2011). Apatinib is a tyrosine kinase inhibitor (TKI) of VEGFR-2, which inhibits tyrosine kinase production by highly selective competition for intracellular ATP binding sites for VEGFR-2, thereby inhibiting the formation of new blood vessels in tumor tissues, thereby achieving antitumor goals (Roviello *et al.*, 2016). Recombinant human endostatin (RHE) is a new biological product of vascular inhibition. Its mechanism of action is to inhibit the formation of tumor angiogenesis by inhibiting the migration of endothelial cells that form blood vessels, thus blocking the nutritional supply of tumor, and thus inhibiting tumor proliferation or metastasis (Li *et al.*,

2018) With the in-depth research of these three targeted drugs, there is still a lack of complete practice in the clinical effects on elderly patients with gastric cancer (Li *et al.*, 2019). Therefore, this experiment is to explore the clinical effects of three targeted drugs, namely, bevacizumab, apatinib and RHE, on elderly patients with gastric cancer, to provide theoretical basis for the molecular-targeted therapy for this disease, bring in reference for clinical diagnosis, and improve the response rate.

MATERIALS AND METHODS

General Data

200 patients with metastatic gastric cancer who came to our hospital between January 2017 and January 2020 were selected and randomly divided into four groups with 50 patients in each group. Three of these four groups were treated with bevacizumab, apatinib and RHE, in respective. The other group was set as control group with no targeted drug for therapy. Among the 200 research objects, 137 are male and 63 are female, aged between 60 and 79. There was no statistical difference in the comparison of general information such as age and sex between the groups of patients ($P > 0.05$), so comparative studies could be carried out.

Selection Criteria

(1) Patients met the clinical diagnostic criteria for gastric cancer (Ono *et al.*, 2016); (2) 60~80 years old; (3) Patients had complete clinical record; (4) This study was approved by the hospital ethics committee. The patient and his family were aware of the purpose and process of

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this study, accepted the treatment plan, and signed an informed consent.

Exclusion Criteria

(1) Patients with hepatitis A, B, C, D, E virus; (2) Patients infected with HIV; (3) Patients with other malignant tumors; (4) Patients with autoimmune diseases; (5) Secondary hypertension caused by kidney disease, endocrine disease, etc.; (6) Patients who had mental or other cognitive impairments or refused to cooperate with the experimenter; (7) Allergic constitution or patients with allergies to various drugs; (8) Patients with liver dysfunction; (9) Patients who had suffered severe trauma and surgery; (10) Patients with chronic infections.

Treatment Methods

Researcher Grouping: Divided into 4 groups according to the double-blind principle; The first group of researchers was responsible for screening and randomly assigning test objects; The second group was responsible for implementing intervention treatment; The third group is responsible for the collection of indicator data; The fourth group was responsible for data collation, statistical analysis and article writing. Operations of each group are confidential to researchers of other groups.

Control group. Totally 50 gastric cancer patients treated with Irinotecan (Shandong Roxin Pharmaceutical Group Co., LTD., National Drug approval H20113455, specification: 2ml: 40mg) was set as control group. An intravenous infusion of 80mg/m² was given within 90 minutes, once a day, for 15 consecutive days as a course of treatment.

Group I. Totally 50 gastric cancer patients treated with bevacizumab on basis of control group was set as Group I. Bevacizumab (specification: 100mg/4ml, manufacturer: Roche Pharmaceutical Ltd.) should be diluted through aseptic technique by a professional doctor: Drew at a dose of 5mg/kg, diluted to 100 ml of 0.9% NaCl injection, discarded the remainder, and no particles or discoloration could be observed by naked eyes. The diluted solution should be stored at 0-8°C for no more than 8 hours. After chemotherapy, the diluent was injected intravenously. The first injection lasted for over 90 minutes without adverse tolerance, and the second injection could be injected for over 60 minutes without adverse tolerance. After that, it could be injected for over 30 minutes.

Group II. Totally 50 gastric cancer patients treated with apatinib on basis of control group was set as Group II. All patients in this group failed chemotherapy and took apatinib (apatinib mesylate tablet) (specification: 0.25g, manufacturer: Jiangsu Hengrui Pharmaceutical Ltd., NMPA Approval Number H20140103) orally after the progression of the disease. Patients took 850mg with warm water half an hour after meal and took once a day for continuous use. If the patient had intolerance or

adverse reactions above grade III, the drug should be discontinued or reduced according to the patient's condition.

Group III. Totally 50 gastric cancer patients treated with recombinant human endostatin (RHE) on basis of control group was set as Group III. The RHE (specification: 15mg/3ml, manufacturer: Shandong Simcere Medgenn Pharmaceutical Ltd., NMPA Approval Number S20050088) was injected intravenously by a professional doctor: Added the injection to 500ml normal saline, uniformed intravenous drip and lasted for 3-4h. When administering with NP chemotherapy regimen, in the first to fourteen days of the treatment cycle, injection had been done once a day and there was a one-week interval between two cycles of treatment. In most cases there are two to four cycles of the treatment. The use time can be appropriately extended according to the patient's tolerance.

Indicator Observation

Tests of All Patients' Blood Samples, Biomarkers, T Cell Subsets and Other Clinical Test Indicators

Test the patients' VEGF, sVEGFR2, HER2 and T cell subsets CD3+, CD4+, CD8+, CD4+/CD8+, CD4+/CD25+ values.

The Use of RECIST to Evaluate the Therapeutic Effects on Patients' Tumors

RECIST evaluation criterion (Johnson *et al.*, 2019) was used to evaluate the longest diameter of the tumor before and after the implementation of targeted therapy, and the evaluation criteria of the tumor are as follows: Complete Remission (CR): All gastric tumor lesions disappeared; Partial Remission (PR): The longest diameter of the gastric tumor lesions was reduced by at least 30% compared to before targeted therapy; Progressive Disease (PD): The longest diameter of tumor lesions increased by 20% compared to before targeted therapy or new lesions appeared; Stable Disease (SD): the stage between PR and PD. RR of gastric cancer treatment= (CR+PR)/total * 100%.

The Use of Modified Clavien Classification of Complications to Evaluate Patients' Adverse Reaction after the Therapy

According to the evaluation criteria (Lerut *et al.*, 2009) of Class 0-V, statistical analysis of the complications of patients after the therapy had been done: Class 0 means that the patients had no complications after the surgery; Class I means that it is no need for drug intervention; Class II needs drug intervention; Class III needs to use intervention methods other than drugs; Class IV represents life-threatening complications; Class V means death. Adverse reaction rate= (II+III+IV+V)/total * 100%.

STATISTICAL ANALYSIS

The data obtained in this study were statistically analyzed and processed by SPSS20.0 software. A chi-square test was employed for technical data, represented as [% _(n)]. A t-test was for measurement data, represented as ($\bar{x} \pm s$). When $P < 0.05$, the difference is statistically significant.

RESULTS

Comparison of VEGF Level among Patients from Four Groups

After the therapy, the VEGF level of all patients from four groups were significantly better than before the therapy ($P < 0.05$). The VEGF level of Group I, II, III were markedly better than the control group ($t = 7.183, 7.000, 7.149$ respectively, $P < 0.001$), as shown in table 1.

Comparison of sVEGFR2 Level among Patients from Four Groups

After the therapy, the sVEGFR2 level of all patients from four groups were significantly better than before the therapy ($P < 0.05$). The sVEGFR2 level of Group I, II, III were markedly better than the control group ($t = 7.309, 7.117, 7.263$ respectively, $P < 0.05$), as shown in table 2.

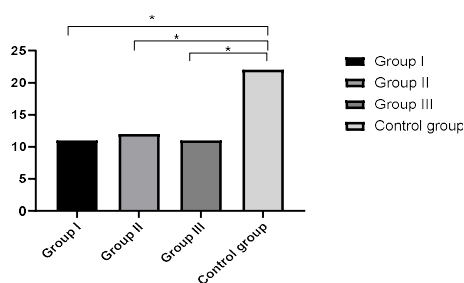
Comparison of HER2 positive detection among Patients from Four Groups

After the therapy, the HER2 positive detection of all patients from Group I, II and III were significantly less than the control group ($P < 0.05$), as shown in fig. 1.

The HER2 positive of the control group after the therapy was: 44% (22/50)

The HER2 positive of Group I, II and III were: 22% (11/50), 24% (12/50), 22% (11/50);

* From top to bottom, the number of HER2 positive after treatment in group I, II, and III was significantly different from that of the control group. ($\chi^2 = 5.473, 4.456, 5.473$, $P = 0.019, 0.035, 0.019$).



Note: The abscissa represents the groups of patients, and the ordinate represents the number of patients

Fig. 1: Comparison of HER2 Positive Proportion

Comparison of T Cell Subsets CD3+, CD4+, CD8+, CD4+/CD8+, CD4+/CD25+ Values of Patients from Four Groups

After the therapy, T Cell Subsets CD3+, CD4+, CD8+, CD4+/CD8+, CD4+/CD25+ Values of patients from

Group I, II and III were markedly better than that of the control group, as shown in table 3.

Comparison of Therapeutic Effects on Patients from Four Groups

After the therapy, the therapeutic effects on patients from Group I, II and III were markedly better than that of the control group ($P < 0.05$), as shown in table 4.

Adverse Reaction of Patients from Four Groups

After the therapy, the adverse reaction rate of patients from Group I, II and III were markedly lower than that of the control group ($P < 0.05$), as shown in table 5.

DISCUSSION

The occurrence and development of most solid tumors are related to tumor angiogenesis. The signal transduction pathway mediated by VEGF and VEGF-2 is a key process in angiogenesis (Khan *et al.*, 2019; Yamaguchi *et al.*, 2016). According to clinical studies, after tumor cells are treated with many targeted anti-angiogenesis drugs, necrosis, density reduction, and tumor hollowing can be found on imaging, while it does not affect the size-changing of tumor cells (Mawalla *et al.*, 2018; Zou *et al.*, 2020). If the previous evaluation standards for therapeutic effects are copied and used for the evaluation of tumor-targeted drugs, the therapeutic effects of targeted drugs will often be underestimated. Therefore, this experiment selected three targeted drugs, bevacizumab, apatinib, and RHE for in-depth research.

Results showed that, after the therapy, the VEGF level and sVEGFR2 level were significantly better than before the therapy, and the VEGF level, sVEGFR2 level, and HER2 positive detection of Group I, II and III were significantly better than that of the control group $P < 0.05$; after the therapy, the therapeutic effects on the tumor in patients from Group I, II and III were markedly better than the control group $P < 0.05$; and the adverse reaction rate of Group I, II and III was obviously lower than that of control group, which had statistical significance. Apatinib is a new type of small molecule tyrosine kinase inhibitor that highly selectively competes for the ATP binding site of VEGF -2 in cells, blocks downstream signal transduction, to inhibit neovascularization in tumor tissue (Li *et al.*, 2018). Bevacizumab, also known as Avastin, has been tested to show that IgG1 antibody can bind to VEGF and block its biological activity to inhibit tumor blood vessel growth (Arjaans *et al.*, 2013). RHE mainly inhibits the migration of vascular endothelial cells to inhibit tumor angiogenesis, thereby blocking the nutritional supply of tumor cells and inhibiting tumor proliferation or metastasis (Liu *et al.*, 2016). RHE mainly inhibits the migration of vascular endothelial cells to inhibit tumor angiogenesis, thereby blocking the nutritional supply of tumor cells and inhibiting tumor proliferation or metastasis (Liu *et al.*, 2016).

Table 1: Comparison of VEGF Level ($\bar{x}\pm s$)

Groups	Before Therapy	After Therapy	t	P
I	449.08±155.11	230.92±96.53	8.4438	<0.001
II	453.19±152.46	235.41±95.71	8.5546	<0.001
III	447.58±153.07	232.45±95.27	8.4372	<0.001
Control Group	451.24±154.06	387.46±120.13	2.3086	0.0231

Table 2: Comparison of sVEGFR2 Level ($\bar{x}\pm s$)

Groups	Before Therapy	After Therapy	t	P
I	450.74±151.07	231.31±96.08	8.6665	<0.001
II	452.86±154.18	235.78±95.66	8.4598	<0.001
III	448.61±150.94	233.09±94.89	8.5477	<0.001
Control Group	455.32±153.52	391.03±121.01	2.3256	0.0221

Table 3: Comparison of T Cell Subsets CD3+, CD4+, CD8+, CD4+/CD8+, CD4+/CD25+ Values ($\bar{x}\pm s$)

Groups	CD3+	CD4+	CD8+	CD4+/CD8+	CD4+/CD25+
I	1.33±0.31	0.99±0.21	0.52±0.11	1.59±0.31	5.81±2.09
II	1.38±0.30	0.98±0.22	0.49±0.14	1.61±0.30	5.46±2.11
III	1.41±0.33	0.99±0.23	0.51±0.12	1.58±0.33	5.76±2.07
Control Group	0.82±0.11	0.49±0.14	0.86±0.26	0.65±0.23	11.88±4.33
tI	10.9633	14.0083	8.5159	17.2195	8.9270
tII	12.3925	13.2869	8.8599	17.9573	9.4246
tIII	11.9935	13.1306	8.6426	16.3485	9.0168

Table 4: Comparison of Therapeutic Effects

Groups	CR	PR	SD	PD	RR
I	0% (0/50)	74% (37/50)	24% (12/50)	2% (1/50)	74% (37/50)
II	0% (0/50)	72% (36/50)	24% (12/50)	4% (2/50)	72% (36/50)
III	0% (0/50)	76% (38/50)	24% (12/50)	0% (0/50)	76% (38/50)
Control Group	0% (0/50)	52% (26/50)	22% (11/50)	26% (13/50)	52% (26/50)
χ^2_{I/P_I}					5.1909/0.023
$\chi^2_{II/P_{II}}$					4.2445/0.039
$\chi^2_{III/P_{III}}$					6.2500/0.012

Table 5: Adverse Reaction of Patients from Four Groups

Groups	Class II	Class III	Class IV	Class V	Rate of Complications
I	8% (4/50)	4% (2/50)	6% (3/50)	0% (0/50)	18% (9/50)
II	2% (1/50)	4% (2/50)	12% (6/50)	2% (1/50)	20% (10/50)
III	6% (3/50)	4% (2/50)	4% (2/50)	0% (0/50)	14% (7/50)
Control Group	6% (3/50)	24% (12/50)	10% (5/50)	6% (3/50)	26% (23/50)
χ^2_{I/P_I}					9.0074/0.003
$\chi^2_{II/P_{II}}$					7.6435/0.006
$\chi^2_{III/P_{III}}$					12.1905/≤0.001

The results of this study are consistent with the results of Piotr Kulig and others (Kulig *et al.*, 2020; De *et al.*, 2015). They stated that “targeted drugs such as apatinib have a significant inhibitory effect on patients with advanced gastric cancer, which can effectively alleviate the patient’s condition and inhibit tumor growth. It greatly reduces the occurrence of postoperative complications, which is conducive to the postoperative recovery of patients.”

On the basis of experiment results, we can conclude that tumor biotherapy represented by molecular targeted drugs has shown an encouraging prospect in oncotherapy. It has

significant clinical effects on the treatment of gastric cancer, can effectively inhibit tumor growth and reduce the occurrence of complications. It is worthy of clinical application and promotion due to its significant therapeutic value for patients with gastric cancer.

CONCLUSION

Our findings revealed that molecular targeted drugs including bevacizumab, apatinib, and recombinant human endostatin showed an encouraging prospect in on gastric cancer.

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