Tropical Journal of Pharmaceutical Research August 2021; 20 (8): 1715-1720
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v20i8.24

Original Research Article

Effect of apatinib combined with chemotherapy on quality of life and related complications in patients with advanced gastric cancer

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Sent for review: 16 April 2021 *Revised accepted: 27 July 2021*

Abstract

Purpose: *To investigate the effect of apatinib combined with chemotherapy on quality of life (QOL) and related complications in patients with advanced gastric cancer (AGC).*
Methods: *Clinical data for 102 AGC patients treated in The Affiliated Hospital of Hebei University (January 2018 - December 2019) were retrospectively analyzed. The subjects were randomly and equally split into chemotherapy group and combination group. Both groups of patients were treated with 180 mg/m^2 of paclitacel, and patients in the combination group were additionally given 500 mg of apatinib daily, for a treatment time to disease remission in both groups. Clinical efficacy, QOL, complications as well as serum SIL-2R, VEGF and TNF-α levels in the two groups were compared to analyze the effect of apatinib combined with chemotherapy on AGC patients.*
Results: *Disease control rate (DCR) and overall response rate (ORR) of gastric cancer patients in the combination group were notably higher than those in the chemotherapy group ($p < 0.05$). After treatment, the serum SIL-2R, VEGF and TNF-α levels in the two groups decreased significantly, of which the levels in the combination group were clearly lower ($p < 0.05$). No notable difference in the incidence of complications was observed between the two groups ($p > 0.05$). After treatment, the QOL scores of both groups increased significantly, of which QOL score in the combination group was notably higher ($p < 0.05$).*
Conclusion: *Apatinib combined with chemotherapy effectively enhances the clinical efficacy of AGC patients, controls the overexpression of serum SIL-2R, VEGF and TNF-α, and improves the QOL of patients without increasing adverse reactions. Therefore, the combination therapy is safe and effective.*

Keywords: *Gastric cancer, Quality of life (QOL), Complications, Apatinib, Chemotherapy*

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INTRODUCTION

Gastric cancer (GC) is a clinically prevalent gastric malignant tumor with the highest incidence in China, which originates from gastric mucosal epithelial cells. According to statistics, GC is one of the most frequently occurring cancers worldwide, with a five-year survival rate of about 20%. With its incidence tends to

increase significantly with age, GC occurs mostly in elderly people aged 50-80 years old [1-4].

According to clinical studies, adenocarcinoma is the most common type of GC in clinic. Adenocarcinoma usually has no obvious adverse symptoms in the early stage, or minor symptoms such as abdominal discomfort, which is often mistaken as chronic diseases such as gastric ulcer. Therefore, the early diagnosis of GC in China remains unsatisfactory. In clinical practice, surgery is the most important treatment method for GC, and it is statistically found that the five-year survival rate of early-stage GC treated by surgery reaches 90.9-100 %. However, effective treatment methods are needed for advanced gastric cancer (AGC) that is mainly treated with chemotherapy to control tumor growth.

In spite of its significant short-term therapeutic effect, chemotherapy can cause strong side effects, thus leading to unsatisfactory long-term effect. At present, the comprehensive treatment program of small molecule targeted drugs combined with chemotherapy has prominent advantages in the treatment of AGC.

Apatinib is a new small molecule antiangiogenic agent that can change the tumor lesions to vacuoles, especially lesions with abundant blood vessels, thus shrinking the tumor [5-8]. Studies have shown that apatinib with chemotherapy in patients can improve the therapeutic effect, mainly because the addition of apatinib can shrink the rumor faster in some patients whose lesions do not significantly or even not shrink after chemotherapy. Therefore, this paper mainly investigated the clinical effect of apatinib combined with chemotherapy on AGC patients.

METHODS

General information on patients

Clinical data for 102 AGC patients treated in the Affiliated Hospital of Hebei University (January 2018 - December 2019) were retrospectively analyzed. The subjects were randomly and equally split into chemotherapy group and combination group.

Inclusion criteria

Patients who were diagnosed with GC by pathological examination, patients with an expected survival time of at least half a year, and patients with complete clinical medical records were included in the study. The study was approved by the hospital ethics committee, and all the patients and their families accepted the treatment plans and signed the informed consent.

Exclusion criteria

Patients with adverse reactions caused by chemotherapy before the study, patients with contraindication to chemotherapy, patients who were allergic to drugs used in the study, patients complicated with other malignant tumors, and those who were unable to cooperate due to mental and other cognitive disorders, or refused to cooperate with the researchers.

Treatments

After maintenance of water and electrolyte balance and acid-base balance, anti-infective therapy and symptomatic treatment, patients in the chemotherapy group were treated with routine chemotherapy, with 21 days as a chemotherapy cycle. They received 175 mg/m2 of paclitaxel (specification:30mg, manufacturer: Beijing SL Pharmaceutical Co., Ltd.; National Medical Products Administration approval no. H20066640) by intravenous drip 3 hour on the first day of the chemotherapy cycle [9,10]. Timely treatment methods such as venous cannula, arterial cannula or regional perfusion were carried out to patients according to the development of the disease.

In addition to the treatment above, patients in the combination group orally took 500 mg of apatinib (specification: 0.25g; manufacturer: Jiangsu Hengrui Pharmaceutical Co. Ltd; National Medical Products Administration approval no. H20140103) at 30 min after meals, once a day. Apatinib must be taken regularly each day, and could not be supplemented if missed. The dosage should be adjusted according to the doctor's advice if adverse reactions occurred. Both groups of patients were treated until disease remission.

Observation indices

Response Evaluation Criteria in Solid Tumors (RECIST) was used to evaluate the therapeutic effect of AGC. The tumors disappeared for more than four weeks, which was complete response (CR). Total maximum size of the tumor was reduced by more than 30% and lasted for more than four weeks, which was partial response (PR). The total maximum size of the tumor was reduced by less than 30% or increased by more than 20%, and lasted for more than four weeks, which was stable disease (SD). Total maximum size of the tumor was increased by more than 20%, which was progressive disease (PD).

DCR = {(CR+PR+SD)/N}100 ..... (1)

ORR = {(CR+PR)/N}100 ..... (2)

where: DCR = disease control rate of GC; ORR = overall response rate; N = total number of patients; CR = complete response; PR = partial response; and SD = stable disease.

Serum SIL-2R, VEGF and TNF-α levels, and complications were observed. The possible complications included hypertension, gastrointestinal reaction, skin and mucosal reaction, liver function damage, renal impairment, thrombocytopenia, myelosuppression and hemorrhage. *Quality of Life (QOL)Assessment Scale* designed by the hospital was used to evaluate physical health, mental state, social status, family relationship and sleep quality, and a higher score represented higher QOL of the patients.

Statistical analysis

The data from this study were analyzed by SPSS20.0 software, including enumeration and measurement data, and subjected to both Chi square and Students t tests. Differences were considered statistically significant when $p < 0.05$.

RESULTS

Comparison of general data

No notable differences in general data were found between the two groups ($p < 0.05$), see below (Table 1).

Clinical efficacy

Table 2 clearly presented notably higher DCR and ORR of GC in the combination group than the chemotherapy group ($p < 0.05$).

Table 1: General clinical profile of patients

Variable	Chemotherapy group (n=51)	Combination group (n=51)	t/χ^2	*P*-value
Age (years old)	(53.47±7.52)	(52.73±7.26)	0.5056	0.6143
KPS score (points)	(80.21±3.78)	(81.14±3.67)	1.2606	0.2104
Differentiation			0.0600	0.807
Medium	10(19.61)	11(21.57)		
Medium-low	25(49.02)	26(50.98)		
Low	16(31.37)	14(27.45)		
Tumor location			0.0393	0.843
Cardia and fundus of stomach	24(47.06)	25(49.02)		
Antrum	9(17.65)	8(15.69)		
Gastric body	18(35.29)	18(35.29)		
Smoking			0.3529	0.552
Yes	27(52.94)	24(47.06)		
No	24(47.06)	27(52.94)		
Drinking			0.3671	0.545
Yes	29(56.86)	32(62.75)		
No	22(43.14)	19(37.25)		
Gender			0.0448	0.832
Male	35(68.63)	34(66.67)		
Female	16(31.37)	17(33.33)		
Residence			0.2065	0.650
Urban area	37(72.55)	39(76.47)		
Rural area	14(27.45)	12(23.53)		

Table 2: Comparison of clinical efficacy {n (%)}

Variable	Chemotherapy group (n=51)	Combination group (n=51)	χ^2	*P*-value
CR	0(0)	0(0)		
PR	14(27.45)	26(50.98)		
SD	12(23.53)	16(31.37)		
PD	25(49.02)	9(17.65)		
DCR	26(50.98)	42(82.35)	11.2941	0.001
ORR	14(27.45)	26(50.98)	5.9226	0.015

Serum SIL-2R, VEGF and TNF-α levels

After treatment, the serum SIL-2R, VEGF and TNF-α levels in the two groups notably decreased, of which the levels in the combination group were obviously lower ($p < 0.05$, Table 3).

Treatment complications

The two groups did not show notable differences in the incidence of complications ($p > 0.05$), as shown in Table 4.

Quality of life

After treatment, the QOL scores of both groups notably increased, of which the QOL score in the combination group was notably higher ($p < 0.05$, Table 5).

Gastric cancer (GC) is a malignant tumor in the digestive system with complexes causes. Medical studies have repeatedly proposed that the formation of GC is mostly related to the long-term chronic inflammation associated with gastric mucosal tissue [11-14]. People's daily diet, work stress, environmental and genetic factors collectively contribute to the increasing incidence of GC in China. Surgical resection of tumors is currently the main treatment to radically eliminate GC in the early and middle stages, but is not suitable for AGC patients. Due to the severe condition, chemotherapy becomes the main treatment method for AGC patients. Soluble interleukin-2 receptor (SIL-2R), an immune active substance and an interleukin receptor, is a cell growth factor in the immune system, which can bind to IL-2 and reduce its activity.

DISCUSSION

Table 3: Serum SIL-2R, VEGF and TNF-α levels of patients (mean ± SD)

Index		Chemotherapy group	Combination Group	t	*P*-value
SIL-2R (pmol/L)	Before treatment	99.87±18.37	100.02±19.29		
	After treatment	79.35±12.48*	57.12±11.07*	9.5164	<0.001
VEGF (pg/ml)	Before treatment	262.21±14.97	261.85±14.36		
	After treatment	240.55±11.76*	215.82±10.31*	11.2924	<0.001
TNF-α (g/L)	Before treatment	29.36±8.15	29.49±9.23		
	After treatment	25.46±6.14*	18.35±5.21*	6.3055	<0.001

Note: *$P < 0.05$, vs before treatment within the same group

Table 4: Comparison of complications

Variable	Chemotherapy group	Combination group	χ^2	*P*-value
Hypertension	8(15.38)	11(20.75)	0.5107	0.475
Gastrointestinal reaction	12(23.08)	14(26.42)	0.1570	0.692
Skin and mucosal reaction	11(21.15)	10(18.87)	0.0857	0.770
Liver function damage	7(13.46)	8(15.09)	0.0571	0.811
Renal impairment	2(3.85)	3(5.66)	0.1905	0.663
Thrombocytopenia	5(9.62)	4(7.55)	0.1433	0.705
Myelosuppression	3(5.77)	2(3.77)	0.2305	0.631
Hemorrhage	4(7.69)	1(1.89)	1.9507	0.163

Table 5: Comparison of QOL scores

Group	Before treatment	After treatment	t	*P*-value
Chemotherapy	25.3±3.1	37.5±3.6	18.3391	<0.001
Combination	24.5±3.4	42.3±3.2	27.2256	<0.001
t		7.1168		
***P*-value**		<0.001		

If the serum SIL-2R level increases, the immune response induced by IL-2 will be inhibited, thus reducing the immune function, and creating conditions for the proliferation and infiltration of tumor cells. Abnormal overgrowth of blood vessels around tumors is the leading cause of the deterioration of cancer. VEGF, secreted by tumor cells or stromal cells, plays a key role in the process of abnormal vascular growth. When tumors grow, the function of nutrient vessels is abnormally active and the expression level of VEGF increases sharply. Therefore, targeted therapy for VEGF is carried out in clinic to block the abnormal growth of blood vessels and treat GC [15-17].

TNF-α is a pro-inflammatory cytokine that can participate in normal immune response and inflammatory response, showing a high value under the action of malignant tumors. The mechanism of apatinib, a novel "tyrosine kinase" inhibitor, is mainly that apatinib can specifically bind to ATP sites in recipient cells, block and interfere with ATP phosphorylation, block downstream signal transduction, and thus inhibit tumor angiogenesis. Hiroyuki Ohnuma *et al* [18] stated in their study that the ORR and DCR of GC patients treated with chemotherapy alone were only 15.4 and 56.4 % while those of patients treated with apatinib combined with chemotherapy were 50 and 84.4 %, indicating that the combination therapy can effectively improve the therapeutic effect in the treatment of GC. Hiroyuki Ohnuma *et al'* s finding is consistent with this study showing that the DCR and ORR of GC in the combination group were notably higher compared with the chemotherapy group.

After treatment, serum SIL-2R, VEGF and TNF-α levels in both groups obviously decreased, of which the levels in the combination group were obviously lower, indicating that apatinib combined with chemotherapy can effectively improve the tumor immune function of patients and has a high antagonistic effect on abnormal angiogenesis.

There was no significant difference in the incidence of complications between the two groups, suggesting that apatinib combined with chemotherapy does not increase the physical burden of patients, with safety. After treatment, the life quality scores of both groups were significantly higher than those before treatment, and the scores in the combination group were significantly higher than those in the chemotherapy group, suggesting effectively increased QOL in patients.

Limitations of the study

Patients were followed up for a short time, hence there was a lack of information on the survival time of patients in the later period. In addition, since this research is a single-center study using a small sample size, more multi-center studies with larger sample size are required for the validation of the results in this study.

CONCLUSION

Apatinib combined with chemotherapy effectively enhances the clinical efficacy of AGC patients, controls the overexpression of serum SIL-2R, VEGF and TNF-α, and improves the QOL of patients without increasing adverse reactions. Therefore, the combination therapy is safe and effective.

DECLARATIONS

Acknowledgement

This work was supported by Baoding Science and Technology Support Plan Project (no. 2041ZF293).

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. DH and YW designed the study and drafted the manuscript. AZ, ZW and LY were responsible for the collection and analysis of the experimental data. GR, SS and CZ revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. #Dan Hong and Yaning Wei contributed equally to this work.

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