Int J Clin Exp Med 2020;13(2):1253-1260
www.ijcem.com /ISSN:1940-5901/IJCEM0101224

Original Article

The role of apatinib combined with chemotherapy in improving quality of life and levels of inflammatory cytokines of patients with advanced breast cancer

Sijian Wang, Jian Zeng

Department of Gastroenterology Ward II, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

Received August 20, 2019; Accepted January 7, 2020; Epub February 15, 2020; Published February 28, 2020

Abstract: Objective: To explore the role of apatinib combined with chemotherapy in improving quality of life and levels of inflammatory cytokines of patients with advanced breast cancer. Methods: A total of 76 patients with advanced breast cancer admitted to our hospital were enrolled as research objects, and randomly divided into a research group (38 patients) and a control group (38 patients). The research group was treated with apatinib combined with chemotherapy, while the control group was administrated with apatinib alone. The two groups were observed in efficacy and incidence of adverse reactions after treatment, and the levels of their serum tumor markers including carcino-embryonic antigen (CEA), carbohydrate antigen 125 (CA125) and carbohydrate antigen 153 (CA153) were determined using chemiluminescence immunoassay before and after treatment; the serum concentrations of their inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factorF-α (TNF-α) were detected using enzyme-linked immuno sorbent assay (ELISA) before and after treatment, and their life quality score before and after treatment was recorded using the functional assessment of cancer therapy-breast (FACT-B) scale. Results: After treatment, the research group showed significantly lower serum IL-6 and TNF-α concentrations, serum tumor marker levels, incidence of adverse reactions, and significantly higher total effective rate and life quality score than the control group (all $P<0.05$), and the research group showed no significant difference with the control group in 3-year overall survival rate ($P>0.05$). Conclusion: Apatinib combined with chemotherapy is better than the single use of apatinib in the treatment of advanced breast cancer. It can better inhibit the growth of tumors, and the quality of life after treatment is significantly increased. It also reduces the incidence of adverse reactions after treatment by inhibiting the expression of IL-6 and TNF-α.

Keywords: Advanced breast cancer, apatinib combined with chemotherapy, apatinib, life quality, inflammatory cytokine

Introduction

Breast cancer, a complex disease, is the most common tumor in women [1], and is also the leading cause of death for cancers in women worldwide [2]. According to statistics, the incidence of breast cancer worldwide has been on the rise yearly [3, 4]. Since most surgical patients for breast cancer are already in advanced stage, even if the cancer tissues have been excised, the metastasis of breast cancer is still likely to occur [5]. The cause of breast cancer is not fully understood, so early diagnosis of patients with breast cancer can contribute to early treatment of them and improve their survival rate [6].

Apatinib is a small molecule inhibitor of targeted vascular endothelial growth factor receptor-2 [7] with excellent antitumor activity in malignant tumors, such as breast cancer, gastric cancer, non-small cell lung cancer and hepatocellular carcinoma [8, 9]. In addition to anti-angiogenesis function, apatinib can also intensify chemical sensitization by reversing multidrug resistance [10]. As a pleiotropic cytokine, interleukin-6 (IL-6) plays an important role in immunoregulation, inflammation and tumorigenesis [11]. Previous studies revealed that IL-6 was expressed in a variety of normal cells, but also expressed by a variety of tumor tissues, such as breast cancer, ovarian cancer and prostate cancer [12], and it played an

important role in many aspects of tumor behavior including tumor growth, cell proliferation and apoptosis, angiogenesis and metastasis [13]. As a multifunctional cytokine, TNF-α involves in promoting inflammatory response of cells, and plays an important role in pathogenesis of autoimmune diseases, inflammation, and malignant diseases [14]. A previous study pointed out that TNF-α concentration determined before surgery may be an important parameter reflecting the severity of invasive breast cancer about staging [15]. There have been many studies on the treatment of advanced breast cancer with apatinib, but there are no studies on effects of apatinib on specific efficacy, postoperative life quality, serum inflammatory factors, IL-6 and TNF-α, which could help the improvement of the treatment. This study focused on patients with advanced breast cancer with apatinib, and then observed the role of IL-6 and TNF-α in the treatment, so as to provide a reference for the treatment of patients with advanced breast cancer.

Materials and methods

General materials

A total of 76 patients with advanced breast cancer treated in our hospital from March 2015 to June 2016 were selected as research objects and randomly divided into a research group (38 patients) and an observation group (38 patients). This study has been approved by the Ethical Committee of the First Affiliated Hospital of Guangxi Medical University, and all research objects and their families have been informed of this study, and they have signed an informed consent form.

Inclusion and exclusion

Patients diagnosed with breast cancer based on histopathology [16], with complete clinical data, expected survival time more than 3 months, normal function in important organs, and without contraindications to chemotherapy were included. Pregnant women, lactating women, patients with severe hematopoietic function damage, combined autoimmune disease or severe mental disease, patients without history of other malignant tumors, and those with poor compliance of treatment were excluded.

Treatment methods

Patients in the control group were all treated with apatinib (Jiangsu Heng Rui Pharmaceutical Co., Ltd., item number: H20140103) at a dose of 500 mg once a day for 4 weeks. Apatinib was orally taken after meals.

In addition to the treatment for patients in the control group, patients in the research group were additionally treated with chemotherapy as follows: They were treated with 1000 mg/m^2 of gemcitabine (Jiangsu Hanson pharmaceutical co., ltd., item number: H20030105) in the way of intravenous drip, 40 mg/m^2 each time, once every three weeks, and they were treated with 1000 mg/m^2 of capecitabine tablets (Jiangsu Heng Rui Pharmaceutical Co., Ltd. Item number H20133365) in the way of oral administration, twice a day for 21 days as a cycle, Tegafur Gimeracil Oteracil Potassium Capsule (Shandong Xinshidai Pharmaceutical Co., Ltd., item number: H20080802) in the way of oral administration, 40 mg/time, twice a day for 21 days as a cycle, and 50 mg/m^2 of Etoposide Capsules (Nippon Kayaku Co., Ltd., item number: H20160613) in the way of oral administration, once a day for 2 cycles (21 days as a cycle). If any patient suffered adverse reactions from apatinib, the drugs were reduced or suspended according to his/her situation.

Observation indexes

In terms of efficacy indexes, the research group was observed and recorded after 4 cycles of treatment, and the control group was observed and recorded after 2 cycles of treatment. Complete remission referred to the result that the lesion disappeared completely after treatment, and the tumor marker detection values were within the normal range. Partial remission referred to the result that the lesion length of patients was shortened by more than 50% after treatment. Stability referred to the result that the lesion length was reduced by 20%-30% after treatment. Progression referred to the result that the lesion length was increased by 20%, or a new lesion occurred. Effective rate = the number of patients with complete

remission + the number of patients with partial remission/the total number of patients ×100%.

The two groups were observed and recorded in adverse reactions after treatment and their life quality before and after treatment was observed and assessed using the functional assessment of cancer therapy-breast (FACT-B) scale. Lower score meant lower life quality.

Determination methods

Fasting venous blood (5 mL) was sampled from each research object at 1 d before administration and 24 h after administration, respectively, centrifuged at 1500 r/min for 10 min, and placed in a low temperature refrigerator at -70°C for later analysis. Enzyme-linked immuno sorbent assay (ELISA) was adopted to determine the concentrations of IL-6 (from Wuhan Elabscience Biotechnology Co., Ltd., item number: E-EL-H0102c) and TNF-α (from Wuhan Elabscience Biotechnology Co., Ltd., item number: E-EL-H0109c) in strict accordance with kit instruction. The serum tumor markers were determined as follows: Fasting venous blood (5 mL) was sampled from each research object at 1 d before administration and 24 h after administration, respectively, centrifuged at 1500 r/min for 10 min, and then their serum CEA, CA125, and CA153 levels were detected using a full-automatic chemiluminescence immunoassay analyzer (Wuhan Easydiagnosis Biomedicine Co., Ltd., item number: CF10).

Follow-up study

The 76 patients were followed up for 3 years by telephone and visiting, one follow-up in each 3 months within the 3 years averagely. No patient was lost to follow-up.

Statistical analysis

Analysis was performed using statistical software, SSPSS22.0 (SPSS, Inc., Chicago, IL, USA). Data about separate groups were counted in the number of cases/percentage [n (%)] and analyzed using chi-square test. Those with theoretical frequency in chi-square test less than 5 were analyzed using continuity correction chi square test. Measurement data were expressed in mean ± standard deviation. Measurement data about comparison between groups were subject to t test, and data about comparison within groups before and after treatment were subject to paired t test. The pictures about overall survival (OS) of patients with advanced breast cancer were drawn using the Kaplan-Meier method, and the OS of them were compared using log-rank. P<0.05 indicated a significant difference.

Results

General information

There is no significant difference between the two groups in clinical baseline data including age, weight, place of residence, nationality, educational background, menstruation, metastatic site, TNM stage, hormone receptor (+), breast cancer type, smoking history, drinking history, and allergic reaction (all P>0.05) (**Table 1**).

Comparison in serum IL-6 concentration before and after treatment

Before treatment, the two groups showed no difference in serum IL-6 concentration (P> 0.05); after treatment, the two groups showed significantly lower serum IL-6 concentration than that before treatment (P<0.05), and the research group showed significantly lower serum IL-6 than the control group (P<0.05) (**Table 2**).

Comparison in serum TNF-α concentration before and after treatment

Before treatment, the two groups showed no difference in serum TNF-α concentration (P> 0.05); after treatment, the two groups showed significantly lower serum TNF-α concentration than that before treatment (P<0.05), and the research group showed significantly lower serum TNF-α than the control group (P<0.05) (**Table 3**).

Comparison in tumor markers before and after treatment

Before treatment, the two groups showed no difference in CEA, CA125 and CA153 (all P> 0.05); after treatment, the two groups showed significantly lower CEA, CA125 and CA153 than those before treatment (all P<0.05), and the research group showed significantly lower CEA, CA125 and CA153 than the control group (all P<0.05) (**Table 4**).

Table 1. General data of patients in the two groups [n (%)] ($\bar{x} \pm sd$)

Category	Research group (n=38)	Control group (n=38)	t/χ^2	P
Age (Y)	44.16±6.27	43.39±8.34	0.651	0.455
Weight (kg)	22.34±3.18	22.15±3.13	0.794	0.263
Place of residence			0.220	0.639
Urban area	22 (57.89)	24 (63.16)		
Rural area	16 (42.11)	14 (36.84)		
Nationality			0.482	0.488
Han nationality	20 (52.63)	23 (60.53)		
Minority nationality	18 (47.37)	15 (39.47)		
Education background			0.881	0.348
≥ Senior high school	25 (65.79)	21 (55.26)		
< Senior high school	13 (34.21)	17 (44.74)		
Menstruation			0.226	0.634
Menopause	13 (34.21)	15 (39.47)		
Premenopause	25 (65.79)	23 (60.53)		
Metastatic site			0.909	0.823
liver	9 (23.68)	11 (28.95)		
Lung	7 (18.42)	5 (13.16)		
Lymph node	12 (31.58)	14 (36.84)		
Brain	10 (26.32)	8 (21.05)		
TNM stage			1.648	0.649
Stage I	11 (28.95)	9 (23.68)		
Stage II	10 (26.32)	11 (28.95)		
Stage III	8 (21.05)	12 (31.58)		
Stage IV	9 (23.68)	6 (15.79)		
Hormone receptor (+)			0.216	0.642
Estrogen receptor (ER)	15 (39.47)	17 (44.74)		
Progesterone receptor (PR)	23 (60.53)	21 (55.26)		
Breast cancer type			0.062	0.803
Ductal carcinoma	27 (71.05)	26 (68.42)		
Lobular carcinoma	11 (28.95)	12 (31.58)		
Smoking history			0.226	0.634
Yes	15 (39.47)	13 (34.21)		
No	23 (60.53)	25 (65.79)		
Drinking history			0.905	0.342
Yes	22 (57.89)	26 (68.42)		
No	16 (42.11)	12 (31.58)		
Allergic reaction			0.220	0.639
Yes	16 (42.11)	14 (36.84)		
No	22 (57.89)	24 (63.16)		

Comparison between the two groups in efficacy after treatment

The effective rate was higher in the research group than in the control group after treatment (P<0.05) (**Table 5**).

Comparison between the two groups in incidence of adverse reactions after treatment

The total incidence of adverse reactions of the research group was significantly lower than that of the control group after treatment (P< 0.05) (**Table 6**).

Comparison between the two groups in life quality score before and after treatment

The research group showed significantly higher life quality score than the control group after treatment (P< 0.05) (**Figure 1**).

Comparison between the two groups in 3-year overall survival rate based on follow-up

The follow-up results revealed that the research group and control group showed no significant difference in 3-year overall survival rate (31.58% or 12/38 vs. 21.05% or 8/38, P>0.05) (**Figure 2**).

Discussion

Breast cancer, the second leading cause of cancer-related death in women [17], is a complex disease with increasing annual incidence and mortality [18], whose risk increase is related to menarche age, menopause and late trimester of full-term pregnancy [19]. It is characterized by the unique metastasis pattern of regional lymph nodes in bone marrow, liver and lung [20].

Apatinib is an orally administrable antiangiogenic drug that can prevent tumor growth [21].

Table 2. Comparison between the two groups in serum IL-6 concentration before and after treatment ($\bar{x}$ ± sd)

Group	n	IL-6 (ng/ml)		t value	*P* value
		Before treatment	After treatment		
Research group	38	228.47±57.21	109.53±36.29	10.820	<0.001
Control group	38	229.85±56.98	148.36±43.64	6.999	<0.001
t value	-	0.916	4.217	-	-
P value	-	0.105	<0.001	-	-

Table 3. Comparison between the two groups in serum TNF-α concentration before and after treatment ($\bar{x}$ ± sd)

Group	n	TNF-α (pg/ml)		t value	*P* value
		Before treatment	After treatment		
Research group	38	82.81±19.97	31.97±9.67	14.120	<0.001
Control group	38	82.17±19.96	36.77±9.98	12.540	<0.001
t value	-	0.139	2.129	-	
P value	-	0.889	0.037	-	

Previous studies revealed that apatinib prolonged the progression-free survival rather than post-progression survival in treatment, which in turn increased the overall survival rate, so it was an effective remedial drug for patients with advanced breast cancer who had experienced failed treatment [22, 23]. Zhu et al. found that apatinib showed acceptable toxicity in the treatment of advanced breast cancer, and apatinib combined with chemotherapy could provide greater clinical benefits for patients with advanced breast cancer [24]. In the study by Zhou et al., with controllable side effects in treatment of mammary spindle cell carcinoma and good tolerance in patients, apatinib was a safe and effective oral targeting drug, especially suitable for patients with chemotherapy failure or poor physical condition [25]. The results of this study revealed that after treatment, the two groups showed significantly decreased serum tumor markers, and the research group showed significantly lower serum tumor markers than the control group, which indicated that apatinib combined with chemotherapy could more effectively inhibit tumor growth, reduce the secretion and synthesis of tumor markers, and inhibit the formation of tumor vessels than apatinib alone. The research group showed significantly higher total effective rate than the control group, which indicated that apatinib combined with chemotherapy had better curative effect and higher disease control effect than apatinib alone in the treatment of advanced breast cancer. Both the two groups showed different degrees of adverse reactions, but the research group showed significantly lower incidence of adverse reactions than the control group, which may be related to the patients' frequent chemotherapy and insensitivity to chemotherapy or drug resistance. The adverse reactions after treatment of the two groups could be relieved or tolerated, indicating that the adverse reactions of apatinib in the treatment of advanced breast cancer were within the controllable range. The research group showed significantly higher life quality score than the control group, which indicated that apatinib combined with chemotherapy could more effectively improve patients' life quality after treatment of advanced breast cancer than apatinib alone. After that, we followed up the mortality of the two groups for 3 years after treatment, and found that the 3-year overall survival rate of the two groups was not different, which indicated that both apatinib combined with chemotherapy and apatinib alone were a feasible scheme in the treatment of advanced breast cancer.

IL-6 is a pleiotropic cytokine with great significance in human immunoregulation, whose serum concentration increase is common in cancer patients, especially in advanced cancer patients, and is associated with poor prognosis of various types of cancer, such as metastatic breast cancer, ovarian cancer, pancreatic cancer, etc. [26]. Previous studies revealed that IL-6 level was the key to the prognosis of patients with breast cancer [27]. As a key participant in tumor microenvironment, TNF-α participates in the pathogenesis of breast cancer [28]. In the study by Janairo et al., apatinib may be used as a radiosensitizer to enhance the clinical efficiency of radiotherapy in liver cancer, increase the level of enzyme and non-enzyme antioxidant, and reduce the levels of inflammatory markers, IL-6, TNF-α and IL-1b [29]. The results of this study revealed that

Table 4. Comparison between the two groups in tumor markers before and after treatment ($\bar{x} \pm sd$)

Group	n	CEA/pg·mL-1		CA125/U·mL-1		CA153/U·mL-1	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research group	38	58.4±5.4	25.9±3.2	61.4±5.9	25.4±2.8	64.2±6.2	27.2±3.5
Control group	38	57.8±5.2	27.7±3.6	62.1±5.7	28.1±2.9	63.9±6.1	29.9±3.7
t value		0.493	2.304	0.526	4.129	0.213	3.268
P value		0.623	0.024	0.601	<0.001	0.832	0.002

Table 5. Comparison between the two groups in adverse reactions after treatment [n (%)]

Efficacy	Research group (n=38)	Control group (n=38)	χ^2 value	*P* value
Complete remission	30 (78.95)	25 (65.79)	-	-
partial remission	5 (13.16)	3 (7.89)	-	-
Stability	2 (5.26)	6 (15.79)	-	-
Progression	1 (2.63)	4 (10.53)	-	-
Total effective rate	35 (92.11)	28 (73.68)	4.547	0.033

Table 6. Comparison between the two groups in incidence of adverse reactions after treatment [n (%)]

Category	Research group (n=38)	Control group (n=38)	χ^2 value	*P* value
Fatigue	1 (2.63)	2 (5.26)	0.347	0.556
Nausea and vomiting	1 (2.63)	2 (5.26)	0.347	0.556
Diarrhea	1 (2.63)	2 (5.26)	0.347	0.556
Leukopenia	0 (0.00)	1 (2.63)	1.013	0.314
Fever	0 (0.00)	2 (5.26)	2.054	0.152
Rash	0 (0.00)	1 (2.63)	1.013	0.314
Total incidence of adverse reaction	3 (7.89)	10 (26.32)	4.547	0.033

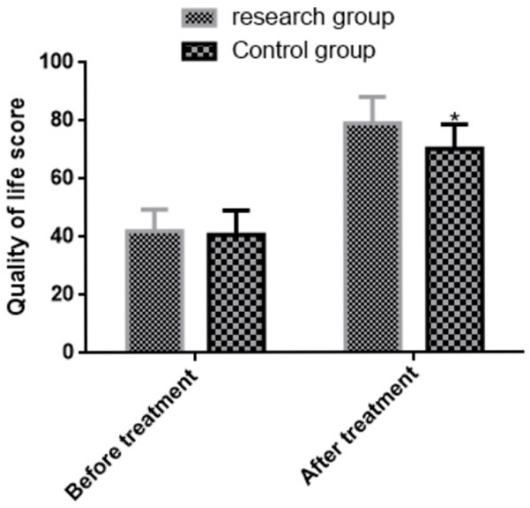

Figure 1. Comparison between the two groups in life quality score before and after treatment. Before treatment, the two groups showed no significant difference in life quality score (P>0.05); after treatment, the research group showed significantly higher life quality score than the control group (P<0.05). Note: *indicates that in comparison with the control group after treatment, P<0.05.

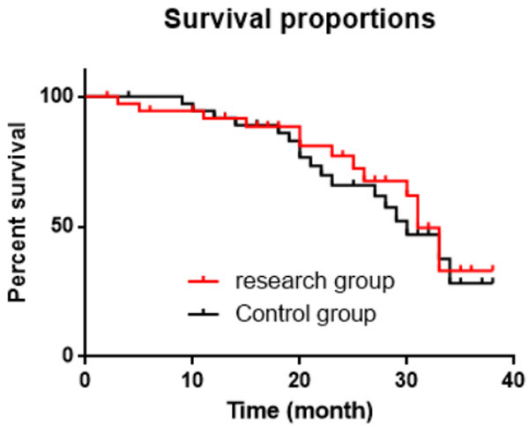

Figure 2. Comparison between the two groups in 3-year overall survival rate after treatment. There was no significant difference between the research group and control group in 3-year overall survival rate (P>0.05).

after treatment, the two groups showed significantly decreased serum IL-6 and TNF-α concentrations, and the research group showed significantly lower serum IL-6 and TNF-α con-

centrations than the control group, which indicated that apatinib combined with chemotherapy could better contribute to prognosis and inhibit inflammatory factor growth than apatinib alone.

This study chose research objects in strict accordance with inclusion criteria and exclusion criteria, so there was no significant difference in clinical baseline data including age, weight, and place of residence between the research group and control group, which ensured the rigor and reliability of the study. Although this study confirmed that apatinib combined with chemotherapy had better clinical efficacy than apatinib alone in the treatment of patients with advanced breast cancer, it did not clarify the regulatory mechanism of apatinib combined with chemotherapy on serum IL-6 and TNF-α, and the number of study cases included were low, so this study had certain limitations. Those inadequacy need to be covered in future research to further corroborate the results of this study.

In conclusion, with advantages in simple and safe oral administration, and ability of inhibiting tumor growth, apatinib combined with chemotherapy is better than apatinib alone in the treatment of patients with advanced breast cancer in efficiency. Although some adverse reactions occurred in the treatment process, they were all within the controllable range. The mechanism of apatinib combined with chemotherapy may be as follows: It inhibits the formation of tumor vessels and accelerates the death of tumor cells by inhibiting the expressions of IL-6 and TNF-α.

Disclosure of conflict of interest

None.

Address correspondence to: Jian Zeng, Department of Gastroenterology Ward II, The First Affiliated Hospital of Guangxi Medical University, No. 6 Shuangyong Road, Nanning 530021, Guangxi, China. Tel: +86-0771-5356100; E-mail: jianzengjianzeng@163.com

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