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Original Article

Clinical efficacy of capecitabine metronomic chemotherapy combined with exemestane for postmenopausal PR-positive breast cancer patients and its influence on tumor markers and immune function

Jing Zhou[1], Zhuo Wang[2]

Departments of [1]Infusion, [2]Breast Surgery, The First People's Hospital of Jingzhou, Jingzhou, Hubei Province, China

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Abstract: Objective: Our aim was to explore the clinical efficacy of capecitabine metronomic chemotherapy combined with exemestane (EXE) in postmenopausal patients with progesterone receptor-positive (PR+) breast cancer and its influence on tumor markers and immune function. Methods: We enrolled 78 postmenopausal patients with PR+ breast cancer who were admitted to the First People's Hospital of Jingzhou and randomly divided them into the research group and control group for 6-months of treatment. The control group was given capecitabine conventional chemotherapy combined with EXE (n = 39), and the research group was treated with capecitabine metronomic chemotherapy combined with EXE (n = 39). After 6 weeks of treatment, the clinical efficacy of the two groups was assessed and compared. The changes in sex hormone indicators (follicle stimulating hormone, luteinizing hormone, estradiol), tumor markers (carcinoembryonic antigen, cancer antigen (CA)-125, CA-153), inflammatory response indicators (tumor necrosis factor-α, interleukin (IL)-8, IL-10), immune function indicators (Ig (immunoglobulin) G, Ig A and Ig M) and the incidence of adverse reactions during treatment were also recorded and compared before and after 6 weeks of treatment. Results: The overall response rate was significantly higher, and the incidence of adverse reactions was markedly lower in the research group than in the control group (both $P < 0.05$). After treatment, the serum levels of follicle stimulating hormone, luteinizing hormone, carcinoembryonic antigen, CA-125, CA-153, tumor necrosis factor-α, IL-8 and IL-10 in both groups decreased while the estradiol levels increased, as compared with those before treatment; the research group showed significantly better results in the above-mentioned indicators than the control group (all $P < 0.05$). Moreover, there was no significant difference in Ig G, Ig A and Ig M after treatment between the two groups, as compared with those before treatment (all $P > 0.05$). Conclusion: Capecitabine metronomic chemotherapy combined with EXE is effective in treating postmenopausal PR+ breast cancer, and can significantly improve sex hormone levels and reduce inflammatory responses. Additionally, it exerts little effect on the body's humoral immune function, which can effectively reduce adverse reactions.

Keywords: Metronomic chemotherapy, capecitabine, exemestane, positive progesterone receptor after menopause, breast cancer, immune function, tumor markers

Introduction

Breast cancer (BC) is the most common form of cancer affecting women, and it is a malignant epithelial tumor of the breast tissue that mainly manifests as breast masses and nipple discharge, which seriously affects the patients' quality of life. Normally, the growth and development of the mammary glands are affected by the inhibition, stimulation, and coordination of multiple hormones. Clinically, more than 50% of breast tumors are hormone-dependent, and the occurrence and development of tumors are regulated by hormones, among which progesterone and estrogen can stimulate the proliferation and growth of breast tumor cells [1, 2]. Progesterone receptor (PR) is highly expressed in postmenopausal BC, and about 60%-70% cases are PR-positive (PR+) [3].

Currently, drug treatment is the main approach for postmenopausal PR+ BC, with the purpose

of prolonging survival time and improving quality of life [4]. Capecitabine conventional chemotherapy can relieve the symptoms of postmenopausal PR+ BC patients, but it also leads to many adverse reactions and some patients are intolerant to it [5, 6]. Metronomic chemotherapy refers to the continuous high-frequency administration of low-dose chemotherapeutic drugs, with the advantages of having definite efficacy and less adverse reactions. In recent years, metronomic chemotherapy has been applied in the clinical treatment of a variety of malignant tumors and it exerts remarkable effects, leading to it being favored by a majority of patients and clinicians [7]. However, there have been few reports on the clinical efficacy of metronomic chemotherapy in patients with PR+ BC. As a result, we preliminarily investigated the clinical efficacy of capecitabine metronomic chemotherapy combined with exemestane (EXE) in postmenopausal patients with PR+ BC patients and its influence on tumor markers and immune function.

Materials and methods

General data

A total of 78 postmenopausal patients with PR-positive breast cancer who were admitted to the First People's Hospital of Jingzhou from August 2017 to March 2019 were selected and divided into the research group (n = 39) and control group (n = 39) by a random number table method. The control group received capecitabine conventional chemotherapy combined with EXE, and the research group was given capecitabine metronomic chemotherapy combined with EXE. All patients were informed of the study and signed a written informed consent, and ethicial approval for the study was given by the Ethics Committee of the First People's Hospital of Jingzhou.

The included patients, aged between 18-70 years old, were diagnosed with PR+ BC according to *New standard guidelines for diagnosis and treatment of common malignant tumors*, and confirmed by pathological examinations [8]. The patients with an expected survival time > 3 months and Karnofsky performance scale (KPS) score ≥ 70 points were also included. Additionally, patients were excluded if they had received metronomic chemotherapy; presented with other malignant tumors, systemic immune diseases, metabolic diseases, coagulation abnormalities, or severe infections; or had poor compliance with treatment. During treatment, patients with recurrence and metastasis or those who died were also excluded.

In the control group, the mean age was 56.9±6.1 years (range 45-69 years), the average disease course was 18.24±2.41 months (range 7-30 months), and there were 11 patients in stage I, 15 in stage II, and 13 in stage III, in terms of clinical stages. In the research group, the mean age was 57.1±5.7 years (range 44-70 years), the average disease course was 18.52±2.53 months (range 8-32 months), and there were 10 patients in stage I, 17 in stage II, and 12 in stage III cases in terms of clinical stages. There was no significant difference in age, disease course, and clinical stage between the two groups (P > 0.05).

Treatment methods

The control group was given conventional chemotherapy with capecitabine (Qilu Tianhe Pharmaceutical Co., Ltd., China), which was administered orally at a dose of 1250 mg/m^2 twice a day, on days 1-14 of a 3-week treatment cycle followed by 7 days of no treatment, and EXE (Zhejiang Medicine Co., Ltd., Xinchang Pharmaceutical Factory, China), which was administered orally at a dose of 25 mg once a day. The research group was given metronomic chemotherapy with capecitabine, which was administered orally at a dose of 500 mg twice a day, and EXE, which was administered orally at a dose of 25 mg once a day. Both groups were treated for a period of 6 weeks.

Outcome measures

After 6 weeks of treatment, the clinical efficacy of the two groups was assessed and compared. The changes in sex hormone indicators (follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2)), tumor markers (carcinoembryonic antigen (CEA), cancer antigen (CA)-125, CA-153), inflammatory response indicators (tumor necrosis factor (TNF)-α, interleukin (IL)-8, interleukin-10), immune function indicators (Ig (immunoglobulin) G, Ig A and Ig M) and the incidence of adverse reactions during treatment were also recorded and compared before and after 6 weeks of treatment.

Table 1. Comparison of clinical efficacy (n, %)

Group	CR	PR	SD	PD	ORR
Control group (n = 39)	3 (7.69)	22 (56.41)	9 (23.08)	5 (12.82)	25 (64.10)
Research group (n = 39)	6 (15.38)	27 (69.23)	4 (10.26)	2 (5.13)	33 (84.62)
χ^2	0.502				4.304
P	0.478				0.038

Note: CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate.

Primary outcomes

Clinical efficacy: Response to the treatment was evaluated as follows. Complete response was defined as the disappearance of all target lesions; partial response was defined as a ≥ 30% decrease in the sum of the longest diameter (SLD) of target lesions, without the appearance of new lesion(s); stable disease was defined as a < 30% decrease or > 20% increase in the SLD of target lesions, without the appearance of new lesion(s); progressive disease was defined as a ≥ 20% increase in the SLD of target lesions, or as the appearance of new lesion(s). The overall response rate was the sum of complete and partial response rate.

Tumor markers: Fasting venous blood (5 mL) was drawn from each patient in the morning before and after treatment, followed by centrifugation and separation of the supernatant. Subsequently, the CEA, CA-125, and CA-153 levels in the supernatant were determined by electrochemiluminescence immunoassay, using a kit purchased from Suzhou Elsbio Co., Ltd., Suzhou, China, strictly according to the manufacturers' instructions.

Immune function indicators: The immunoglobulin (Ig) levels (Ig G, A, and M levels) were measured by immune scatter turbidimetry.

Adverse reactions: Myelosuppression, hand-foot syndrome, and gastrointestinal reactions were evaluated according to the World Health Organization recommendations for grading of acute and subacute toxicity. Myelosuppression was defined as white blood cells < 3.9 * 10^9/L, hemoglobin < 100 g/L, or platelets < 99 * 10^9/L during or after chemotherapy. Hand and foot syndrome referred to limb erythema caused by palmar-plantar dysesthesia or chemotherapy, which mainly manifested as numbness, dysesthesia, paresthesia, tingling, pain, skin swelling, erythema, or desquamation, rhagadia, induration-like blisters and severe pain. Besides, gastrointestinal reactions were defined as the onset of nausea, vomiting, diarrhea, etc. during or after chemotherapy.

Secondary outcomes

Sex hormone indicators: FSH, LH and E_2 levels were determined by electrochemiluminescence immunoassay, using a kit purchased from Suzhou Elsbio Co., Ltd., China, strictly according to the manufacturers' instructions.

Inflammatory response indicators: TNF-α, IL-8, and IL-10 levels were measured by enzyme-linked immunosorbent assay, using a kit purchased from Suzhou Elsbio Co., Ltd., China, and performed strictly in accordance with the manufacturers' instructions.

Statistical analysis

All data analyses were performed with the SPSS 20.0 software. The measurement data were expressed as mean ± standard deviation (x ± sd). Independent t-test was used for the comparison between the two groups, and paired t-test was applied for the comparison within the same group before and after treatment. Chi-square test (χ^2 test) was adopted for the comparison of enumeration data expressed as a percentage (%). P < 0.05 was considered statistically significant.

Results

Comparison of clinical efficacy

The overall response rate in the research group (84.62%, 33/39) was significantly higher than that in the control group (64.10%, 25/39; P < 0.05). See **Table 1**.

Comparison of sex hormone indicators before and after treatment

After treatment, the FSH and LH levels decreased, while the E_2 levels increased in both groups (t ≥ 11.050, P = 0.000), as compared

Table 2. Comparison of sex hormone levels (x ± sd)

Group	Control group (n = 39)	Research group (n = 39)	t	P
FSH (mIU/mL)				
Before treatment	52.36±5.27	52.14±5.18	0.186	0.853
After treatment	38.25±3.08***	29.85±2.84***	12.521	0.000
LH (mIU/mL)				
Before treatment	44.52±4.31	44.19±4.52	0.330	0.742
After treatment	34.85±3.36***	25.36±2.56***	14.030	0.000
E_2 (pmol/L)				
Before treatment	28.96±3.25	29.15±3.05	0.266	0.802
After treatment	48.61±5.07***	69.25±5.62***	8.779	0.000

Note: Compared with the same group before treatment, ***P < 0.001. FSH: follicle stimulating hormone; LH: luteinizing hormone; E_2: estradiol.

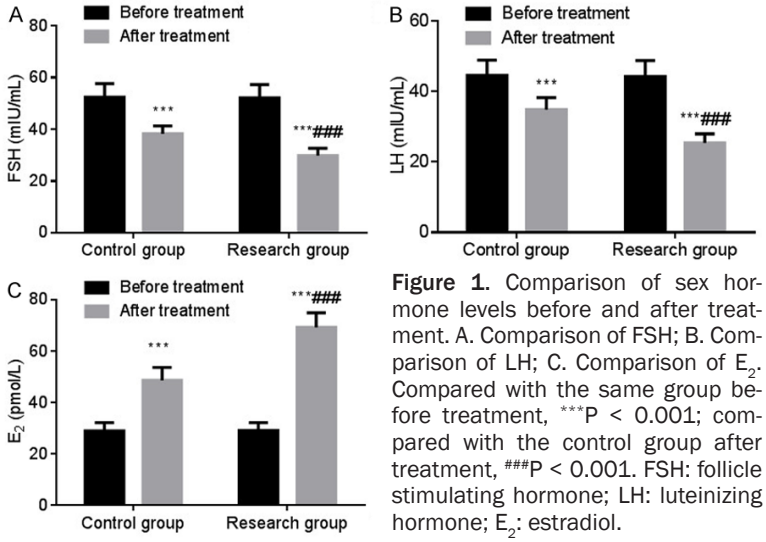

Figure 1. Comparison of sex hormone levels before and after treatment. A. Comparison of FSH; B. Comparison of LH; C. Comparison of E_2. Compared with the same group before treatment, ***P < 0.001; compared with the control group after treatment, ###P < 0.001. FSH: follicle stimulating hormone; LH: luteinizing hormone; E_2: estradiol.

Table 3. Comparison of tumor marker levels (x ± sd)

Group	Control group (n = 39)	Research group (n = 39)	t	P
CEA (ng/mL)				
Before treatment	16.69±2.18	16.87±2.32	0.353	0.725
After treatment	9.25±2.14***	5.34±1.64***	9.057	0.000
CA-125 (U/mL)				
Before treatment	92.36±6.48	92.69±7.21	0.213	0.832
After treatment	52.85±3.36***	35.89±4.24***	19.077	0.000
CA-153 (U/mL)				
Before treatment	72.81±5.21	72.37±5.29	0.370	0.712
After treatment	52.17±4.85***	36.25±3.25***	17.029	0.000

Note: Compared with the same group before treatment, ***P < 0.001. CEA: carcinoembryonic antigen; CA: cancer antigen.

with those before treatment. Besides, FSH and LH levels were lower, and E_2 levels were higher in the research group than in the control group (P < 0.05). See **Table 2** and **Figure 1**.

Comparison of tumor markers before and after treatment

After treatment, the serum CEA, CA-125, and CA-153 levels in both groups were significantly decreased (t ≥ 15.210, P = 0.000), as compared with those before treatment. Moreover, the serum CEA, CA-125, and CA-153 levels in the research group were much lower than those in the control group (P < 0.05). See **Table 3** and **Figure 2**.

Comparison of inflammatory factors before and after treatment

After treatment, the serum TNF-α, IL-8, and IL-10 levels in both groups were significantly decreased (t ≥ 8.685, P = 0.000), as compared with those before treatment. In addition, the serum TNF-α, IL-8, and IL-10 levels were lower in the research group than in the control group (P < 0.05). See **Table 4** and **Figure 3**.

Comparison of immune functions before and after treatment

No significant differences were identified between the two groups regarding Ig G, A and M levels before and after treatment (P > 0.05). See **Table 5** and **Figure 4**.

Comparison of adverse reactions

The research group (7.69%, 3/39) showed a markedly lower incidence of adverse reactions than the control group (30.77%, 12/39; P < 0.05). See **Table 6**.

Discussion

In recent years, the number of BC patients has been increasing in China with a shift towards

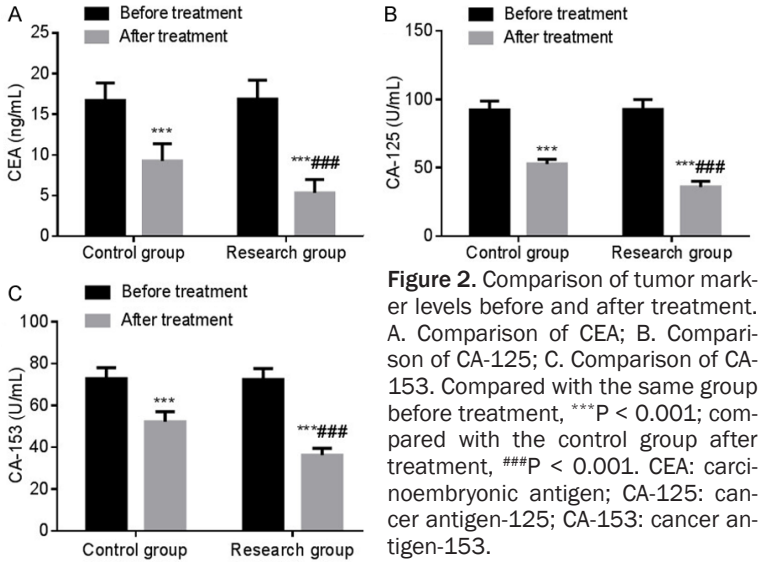

Figure 2. Comparison of tumor marker levels before and after treatment. A. Comparison of CEA; B. Comparison of CA-125; C. Comparison of CA-153. Compared with the same group before treatment, ***P < 0.001; compared with the control group after treatment, ###P < 0.001. CEA: carcinoembryonic antigen; CA-125: cancer antigen-125; CA-153: cancer antigen-153.

younger age groups, which poses a serious threat to women's life and health. Most cases of BCs are hormone-dependent, and PR+ BCs cases are relatively common. Tumor markers are chemicals that can reflect the presence of tumors and help evaluate the therapeutic effect and prognosis [9]. CEA, CA-125, CA-153 are typical tumor markers of breast cancer, among which CEA is a useful tumor marker for metastasis and recurrence, CA-125 is an independent prognostic indicator, while CA-153 is the most important specific marker for diagnosing BC [10, 11]. Guo et al. found that due to the presence of tumors and other factors, lymphocyte nucleic acid synthesis was decreased in postmenopausal PR+ BC patients, which resulted in reduced immune function [12]. Ig G, Ig A and Ig M, are the main antibodies secreted *in vitro* by B lymphocytes, they mediate non-specific humoral immunity and can play a role as indicators of non-specific immune function in the body [13]. As an important constituent of the BC microenvironment, tumor-associated inflammatory cells can secrete vascular endothelial growth factor, epidermal growth factor, TNF and IL, which exert tumor-promoting effects [14]. TNF-α, IL-8, and IL-10 play a role in cell death, chemotaxis, and regulation in the immune-inflammatory response, but in malignant tumors, these inflammatory factors are conducive to tumor cell growth, tumor angiogenesis, and tumor cell escape [15]. Hence, it is important to effectively improve the immune function and reduce the inflammatory

Table 4. Comparison of inflammatory factor levels (x ± sd, pg/mL)

Group	Control group (n = 39)	Research group (n = 39)	t	P
TNF-α				
Before treatment	32.87±3.03	33.18±2.98	0.456	0.650
After treatment	27.63±2.24***	22.25±2.15***	10.821	0.000
IL-8				
Before treatment	26.52±2.81	26.79±2.62	0.439	0.662
After treatment	19.78±1.92***	16.41±2.02***	7.552	0.000
IL-10				
Before treatment	23.24±2.17	23.59±2.07	0.726	0.470
After treatment	18.61±2.03***	14.23±1.82***	10.033	0.000

Note: Compared with the same group before treatment, ***P < 0.05. TNF-α: tumor necrosis factor-α; IL: interleukin.

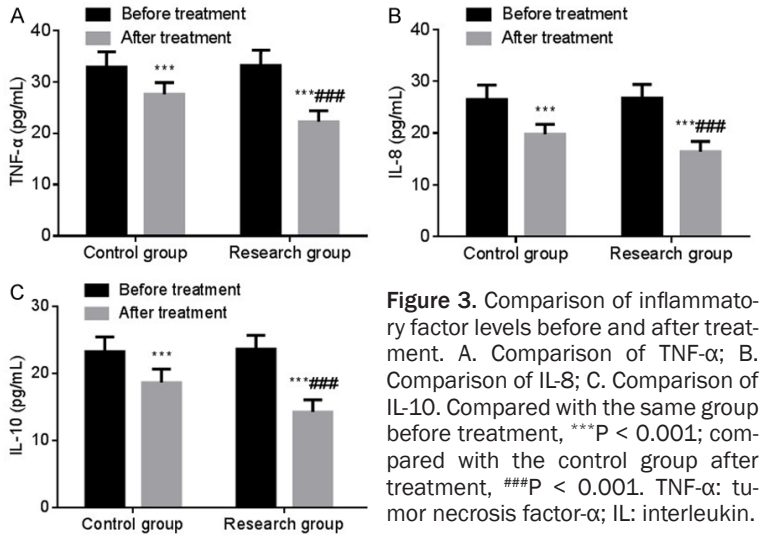

Figure 3. Comparison of inflammatory factor levels before and after treatment. A. Comparison of TNF-α; B. Comparison of IL-8; C. Comparison of IL-10. Compared with the same group before treatment, ***P < 0.001; compared with the control group after treatment, ###P < 0.001. TNF-α: tumor necrosis factor-α; IL: interleukin.

Table 5. Comparison of immune functions (x ± sd)

Group	Control group (n = 39)	Research group (n = 39)	t	P
Ig G (g/L)				
Before treatment	10.25±1.28	10.27±1.21	0.071	0.944
After treatment	10.19±1.18	10.14±1.22	0.184	0.855
Ig A (g/L)				
Before treatment	2.12±0.38	2.15±0.29	0.392	0.696
After treatment	2.14±0.34	2.05±0.15	0.168	0.867
Ig M (g/L)				
Before treatment	1.88±0.57	1.87±0.44	0.173	0.863
After treatment	1.95±0.44	1.85±0.46	0.981	0.330

Note: Ig: immunoglobulin.

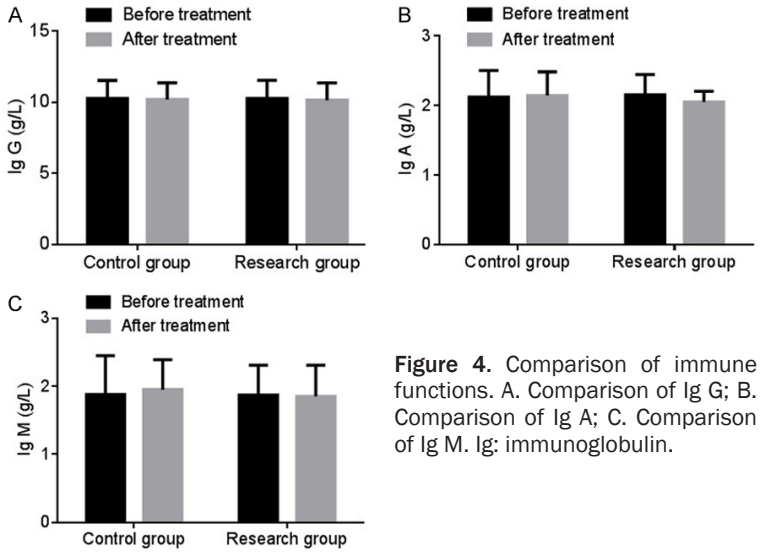

Figure 4. Comparison of immune functions. A. Comparison of Ig G; B. Comparison of Ig A; C. Comparison of Ig M. Ig: immunoglobulin.

response in postmenopausal PR+ BC patients for inhibiting the development of disease and promoting physical recovery.

Our study showed that the overall response rate was higher, and the incidence rate of adverse reactions was lower in the research group than in the control group; both groups showed good results in the serum FSH, LH, E_2, CEA, CA-125, CA-153, TNF-α, IL-8 and IL-10 levels, as compared with those before treatment, while the research group responded with better results than the control group. Li et al. reported that the effect of capecitabine metronomic chemotherapy in the maintenance treatment of elderly patients with metastatic BC was equivalent to that of conventional-dose maintenance therapy, but the metronomic chemotherapy could reduce adverse reactions and improve quality of life [16]. However, we identified that capecitabine metronomic chemotherapy was comparatively effective in PR+ BC patients, which may be related to the selected samples in our study (all PR+ BC patients). The results suggest that capecitabine metronomic chemotherapy combined with EXE can significantly ameliorate clinical efficacy, improve sex hormone levels, reduce inflammatory responses, enhance anti-tumor ability, and inhibit tumor recurrence and metastasis in postmenopausal PR+ BC patients with the advantage of high safety.

Nowadays, endocrine therapy is the mainstay treatment for postmenopausal PR+ BC patients, mainly to reduce or block the secretion of E_2, and its treatment outcome is affected by the sensitivity of tumor cells to hormones and decreased levels of hormones [17]. Most of the E_2 in the blood of postmenopausal PR+ BC patients is derived from the conversion of androgens in the ovaries and adrenal glands by aromatase in peripheral tissues [18]. As an irreversible steroidal aromatase inhibitor, EXE can irreversibly bind to the active site of aromatase and inactivate aromatase with a similar structure to the natural substrate androstenedione, thereby blocking the secretion of E_2 to achieve anti-tumor effects [19, 20]. Capecitabine is a fluoropyrimidine deoxynucleoside carbamate drug that can be converted to the antineoplastic active drug 5-fluorouracil in the human body, exerting a strong antineoplastic effect. On one hand, capecitabine can inhibit cell division, interfere with the synthesis of protein and DNA, and reduce tumor cell proliferation [21]. On the other, it can inhibit the growth and chemotaxis of vascular endothelial cells stimulated by thymidine phosphorylase, suppress tumor angiogenesis, in-duce tumor cell apoptosis, and thus facilitate recovery of physical activity [22]. Nevertheless, conventional chemotherapy is not conducive to the progno-

Table 6. Comparison of adverse reactions (n, %)

Group	Myelosuppression	Hand-foot syndrome	Gastrointestinal reactions	Total cases
Control group (n = 39)	3 (7.69)	4 (10.26)	5 (12.82)	12 (30.77)
Research group (n = 39)	2 (5.13)	0 (0.00)	1 (2.56)	3 (7.69)
χ^2	0.000	2.372	1.625	6.686
P	1.000	0.124	0.202	0.010

sis of postmenopausal PR+ BC patients owing to adverse reactions such as myelosuppression and gastrointestinal reactions caused by a large dose of capecitabine. Metronomic chemotherapy, in contrast, achieves the goal of suppressing tumor neovascularization by high-frequency, continuous and low-dose administration, and targets vascular endothelial cells [23, 24]. Furthermore, continuous administration of metronomic chemotherapy can compensate for the shortcomings of endothelial cell repair during the intermission between conventional chemotherapy, so as to promote the inhibition of tumor cell proliferation and anti-tumor angiogenesis [25].

Meanwhile, our study also demonstrated that there was no significant difference in Ig G, Ig A and Ig M between the two groups before and after treatment, indicating that capecitabine metronomic chemotherapy combined with EXE has little effect on the humoral immune function in treating postmenopausal PR-positive breast cancer.

However, with a relatively small sample size and limited observation time in this preliminary study, we are aware that the results may be biased, and multicenter studies of over 100 cases with 1-year-plus observation time are needed to get a more precise conclusion in the future.

To sum up, capecitabine metronomic chemotherapy combined with EXE is effective in the treatment of postmenopausal PR+ BC, and can significantly improve sex hormone levels, and reduce inflammatory responses and adverse reactions.

Disclosure of conflict of interest

None.

Address correspondence to: Zhuo Wang, Department of Breast Surgery, The First People's Hospital of Jingzhou, No.8 Hangkong Road, Shashi District, Jingzhou 434000, Hubei Province, China. Tel: +86-0716-8111888; E-mail: wangzhuoh8jz@163.com

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