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Role of leuprorelin on ovarian function of patients with receptor-positive premenopausal breast cancer

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Abstract: This study aims to investigate the clinical efficacy of leuprorelin on ovarian function in premenopausal breast cancer (PBC) with positive Estrogen or Progesterone receptor. Forty receptor-positive PBC patients admitted to our hospital from January 2018 to October 2020 were randomized into control group and observation group, with 20 cases in each group. Tamoxifen and tamoxifen plus leuprorelin was respectively applied. The levels of bFSH and bAFC, total effective rate, survival rate at 6, 18 and 30 months, adverse reactions, the quality of life and activity of life scores were recorded and compared. After treatment, bFSH and bAFC in the observation group group were better. The total effective rate was 90.00% in the observation group and 55.00% in the control group. The survival rate of 18 and 30 months in the observation group was notably higher while the incidence of adverse reactions was lower. The quality of life score and activity of life score in the observation group were higher. Leuprorelin combined with endocrine drugs can obviously protect ovarian function with significant long-term effect, which effectively reduces the impact of adverse reactions on receptor-positive PBC patients, with higher safety and better feasibility.

Keywords: Leuprorelin, premenopausal breast cancer patients, ovarian function, receptor positive, adverse reaction.

INTRODUCTION

In China, the incidence rate of breast cancer (BC) is increasing year by year (Li *et al.*, 2016). With the continuous advance of chemotherapy drugs and treatment level, the 5-year survival rate of early BC patients has reached over 95% (Cheng *et al.*, 2019). Moreover, patients have higher requirements for quality of life. Chemotherapy drugs will damage the ovarian function and induce ovarian dysfunction (Giuliano *et al.*, 2019). Due to the high risk of recurrence of premenopausal breast cancer (PBC), the effect of tamoxifen alone has an undesirable outcome (Goto *et al.*, 2019). Leuprorelin is currently a commonly used clinical ovariectomy drug for the treatment of premenopausal breast cancer and prostate cancer (referred to as GnRH drugs) (Han *et al.*, 2019). GnRH drugs are similar to GnRH in structure and compete for pituitary GnRH receptor. When the pituitary GnRH receptor is fully occupied and depleted by GNRH-A, it will produce a down-regulating effect on the pituitary gland (Bui *et al.*, 2020). That is, the gonadotropin secreted by the pituitary gland is reduced, which leads to a significant decrease in the sex hormones secreted by the ovary, similar to surgery to remove the ovary, known as medical oophorectomy. It has been applied to premenopausal breast cancer and estrogen receptor positive patients (Zhang *et al.*, 2017). Therefore, it is necessary to carry out clinical research on tamoxifen combine with other effective drugs in the treatment of PBC, so as to improve the clinical therapeutic effect, further reduce the occurrence of adverse reactions, and ensure the survival status and quality of life of patients. In this study, the effect and clinical efficacy of leuprorelin and endocrine drugs on ovarian function in receptor-positive PBC patients were analyzed.

MATERIALS AND METHODS

General data

Totally 40 patients who were admitted to our hospital owing to receptor-positive PBC from January 2018 to October 2020 were enrolled and randomized into control group and observation group (n=20). Inclusion criteria (Mistry *et al.*, 2018): (1) Patients confirmed as breast cancer pathologically; (2) Immunohistochemical results showed that at least one of estrogen or progesterone receptor is positive; (3) Patients who were not menopausal before treatment; (4) Patients who had received surgery, chemoradiotherapy and other treatments in a standardized manner; (5) This study was approved by the Hospital Ethics Committee of Cangzhou Central Hospital (Approval no. 2017LC102-25); (6) Patients and their families had clearly knew the theme of this study, and independently cooperate with the research content and sign informed consent forms. Exclusion criteria: (1) Patients who did not completed routine adjuvant therapy; (2) Patients who had not reached the follow-up time will terminate treatment by themselves; (3) Patients with the second primary cancer; (4) Incomplete clinical data. (5) Patients complicated with serious neurological diseases, mental state abnormalities or mental classification; (6) Patients complicated with severe heart, kidney, lung and other organ failure diseases; (7) Patients complicated with coagulation dysfunction; (8) Patients who resisted the

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treatment; (9) Patients who participated in other researchers. Randomized comprehensive sequential method was used to divide into control group and observation group, with 20 cases in each group. The patients in the observation group were all female. The age of the patients in the observation group ranged from 29 to 52 years old, with an average of (41.45±5.89) years old. The course of the disease was 1 to 4 years, with an average of (2.2±0.5) years. The age of the control group ranged from 28 to 50 years old, with an average of (41.25±5.75) years old and the course of disease lasted from 1 to 4 years, with an average of (2.3±0.4) years. The baseline data of the two groups were homogeneous (*P*>0.05, table 1).

Methods

The control group received tamoxifen (SFDA approval number H32021472, specification 10mg, Yangzijiang Pharmaceutical Group Co., Ltd.) (10mg/time, twice/d).

The observation group: On the basis of the control group, they received leuprorelin (SFDA approval number H20093852, specification 3.75mg, Shanghai Lizhu Pharmaceutical Co., Ltd.) combined treatment, subcutaneous injection of 3.75mg/time, once every 4 weeks. The treatment was continued for 1 year.

Observing Indicators

The basic follicle stimulating hormone (bFSH) and basic sinus egg count (bAFC) of two groups were compared before and after treatment. The total effective rate, survival rate at 6, 18 and 30 months after operation and the incidence of adverse reactions of the two groups were observed and recorded. The living conditions of the patients were evaluated by quality of life and activity of daily life (ADL) score, and then compared and analyzed. The total effective rate was determined by the therapeutic effect of the patient (Kendzierski *et al.*, 2018). Complete remission: after treatment, the imaging examination results show that the tumor focus is reduced by over 90% and there is no discomfort or pain. Partial remission: The imaging results show that the tumor focus is reduced by about 70%, with slight pain and discomfort, which could be relieved after rest. Stable stage: The tumor focus of the patient shrank by about 40% and shows no signs of malignant transformation. In progression: After treatment, the focus of the patient does not improve or even shows signs of aggravation. The total effective rate of treatment = (complete remission + partial remission + stable)/total number of cases × 100%.

The quality of life score is based on the comprehensive score questionnaire, with a total score of 40 points. The higher the score, the higher the quality of life and vice versa. The score of Activity of Daily Living Scale (ADL) is based on Barthel index, including washing, eating, bathing, dressing, going to the toilet and other items. It is rated with 0, 5, 10 and 15 respectively, with a full score of 100 points (Strini *et al.*, 2020). The higher the score, the better the living activity ability and vice versa.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS 23.0 software. The measurement data were expressed as (mean ± standard error) and independent paired t test was adopted to determine whether there were differences from another group. The count data was expressed as [n (%)] and tested by χ^2. Significance was declared at a P value less than 0.05.

RESULTS

Comparison of bFSH and bAFC before and after treatment

Before treatment, bFSH and bAFC in two groups were similar (*P*>0.05). After treatment, bFSH and bAFC in the observation group were found to be better compared to the control group (*P*<0.05, table 2).

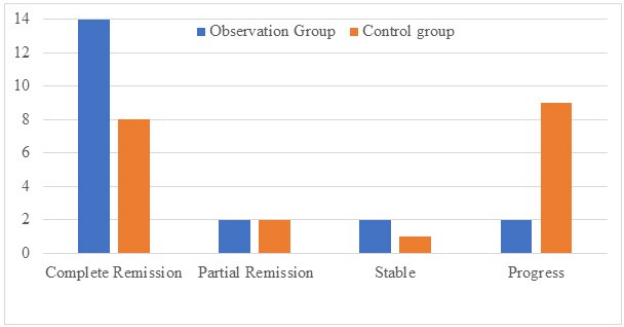

Fig. 1: Comparison of total effective rate between two groups

Comparison of the total effective rate

The total effective rate was 90.00% (18/20) in the observation group and 55.00% (11/20) in the control group. In treatment group, there were 14 cases of complete remission, 2 cases of partial remission, 2 cases at stable stage and 2 cases at progression, while in the reference group, there were 8 cases of complete remission, 2 cases of partial remission, 1 case at stable stage and 9 cases at progression. And the difference reached statistical significance (χ^2=6. 144, *P*=0. 013, table 3, fig. 1).

Comparison of 6, 18 and 30-month survival rates

There was no significant difference in 6-month survival rate between two groups (*P*>0.05). The 18 and 30-month survival rate in observation group were remarkably better when compared against the control group (*P*<0.05, table 4).

Comparison of the incidence of adverse reactions

The incidence of adverse reactions was 15.00% (4/55) in the observation group and 45.00% (16/55) in the control group (*P*<0.05, table 5).

Table 1: Comparison of baseline information

Group	Age (Years old)	Course of disease (year)
Observation Group	41.45±5.89	2.25±0.80
Control group	41.25±5.75	2.16±0.66
t	0.109	0.385
P	0.914	0.703

Table 2: Comparison of bFSH and bAFC between two groups before and after treatment

Group	n	bFSH (IU/L)		bAFC	
		Before treatment	After treatment	Before treatment	Before treatment
Observation Group	20	7.13±1.97	13.30±3.19	11.36±3.21	9.79±2.07
Control group	20	16.52±3.57	16.52±3.57	12.01±3.06	7.03±1.97
t		-0.032	-2.298	-0.650	4.301
P		0.975	0.005	0.520	0.000

Table 3: Comparison of total effective rates between two groups

Group	n	Complete remission	Partial remission	Stable		Total effective rate
Observation Group	20	14	2	2	2	18 (90.00)
Control group	20	8	2	1	9	11 (55.00)
χ^2						6.144
P						0.013

Table 4: Comparison of survival rates at 6, 18 and 30 months after operation between the two groups [(n)%]

Group	n	6 months after operation	18 months after operation	30 months after operation
Observation Group	20	18 (90.00)	17 (85.00)	15 (75.00)
Control group	20	16 (80.00)	11 (55.00)	8 (40.00)
χ^2		0.784	4.286	5.013
P		0.376	0.038	0.025

Table 5: Comparison of adverse reaction incidence

Group	n	Decrease of bone mineral density	Endometrial thickening	Jaundice	Incidence of adverse reactions
Observation Group	20	1	1	1	3 (15.00)
Control group	20	4	3	2	9 (45.00)
χ^2					4.286
P					0. 038

Table 6: Comparison of quality of life score and ADL score

Group	n	Quality of life score	ADL score
Observation Group	20	30.75±0.32	76.03±0.32
Control group	20	20.80±0.45	61.40±0.45
t		78.536	0.000
P		0.000	0.000

Comparison of quality of life score and ADL

The quality of life score and ADL score in the observation group were observed to be remarkably higher (P<0.05, table 6).

DISCUSSION

The incidence of male BC has risen over the past few decades (Hansra *et al.*, 2020), and it would overwhelmingly threaten the patient's health and even life in serious cases (Park *et al.*, 2019). Over 1.6 million people are diagnosed with cancer and 1.2 million people die of cancer every year in China. Every year, the number of new cases and deaths of BC in China account for 12.2% and 9.6% of the world's total, respectively (Han and Youn *et al.*, 2019; von Hippel *et al.*, 2019). Since Halsted's standard radical surgery for BC issued in 1894, the treatment was carried out according to tumor stages, the risk degree was determined by combining immunohistochemical phenotype and clinicopathological

classification, and then treatment options were made referring to molecular pathology and molecular typing at gene level. PBC bears a high risk of recurrence due to its biological characteristics. Receptor-positive PBC patients rely more on endocrine drug therapy after completing surgery and conventional radiotherapy and chemotherapy (Goto *et al.*, 2017; Kurebayashi *et al.*, 2017; Ozaki *et al.*, 2018; Zhu *et al.*, 2016). Notably, BC is particularly common (Sansone *et al.*, 2016) in premenopausal women, whose endocrine conditions will change, leading to endocrine disorders, emotional instability, immunity decline, and increasing the possibility of illness. Currently, the surgery, radiotherapy and chemotherapy remain the mainstay of BC treatment, but drugs are still needed to enhance the curative effect (Tanios *et al.*, 2017).

Tamoxifen is a non-steroidal anti-estrogen drug widely used in the clinical practice of breast cancer, and is also a synthetic anti-estrogen drug. It can be used for both premenopausal and postmenopausal patients (Hannah-Shmouni *et al.*, 2018). Its main mechanism of action lies in its structure similar to estrogen, which can compete with estrogen receptor with estradiol. Through the combination with estrogen receptor, it can also stimulate the growth factor and angiogenic factor of tumor cells through secretion mechanism, thus inhibiting the growth and development of cancer cells and achieving therapeutic effect. However, due to the stimulation of drug effect in clinical treatment, it has greater odds of adverse reactions such as endometrial hyperplasia and bone density reduction, which is not conducive to long-term medication (Kojima *et al.*, 2018). Leuprorelin is a gonadotropin drug used as leuprorelin acetate injection in clinical drugs for the treatment of breast cancer, because the performance of leuprorelin acetate at indoor temperature remains more stable, and leuprorelin acetate is ineffective after oral administration, so it needs subcutaneous injection to exert its efficacy. Its mechanism of action lies in the inhibition of pituitary-gonad system, thus reducing the secretion of sex hormones and keeping stable low estrogen level in patients for a long time (Lee *et al.*, 2021).

In the present study, we found that before treatment, bFSH and bAFC in the two groups were similar (P> 0.05). After treatment, bFSH and bAFC in the observation group were significant greater (P<0.05). The possible mechanisms are as follows. (1) The reduction of the number of primordial follicles entering the follicle leads to the reduction of estrogen level in the body and ovarian perfusion, then diminishes the destructive impact of chemotherapy drugs and block follicular cell apoptosis, and this process is reversible; (2) Ovarian function can be protected by storing primordial follicles and the sensitivity of developing follicles to chemotherapy drugs can be reduced. In this study, the observation group' total effective rate (90.00%) was notably higher, and the incidence rate of adverse reactions (15.00%) was notably lower. After treatment, the quality of life and state of the treatment group are obviously improved, and the survival rate is improved. It is confirmed that the combination of the two drugs can expand the effects of the two drugs, with higher safety and quality of life.

CONCLUSION

From this study, leuprorelin combined with endocrine drugs can obviously protect ovarian function with significant long-term effect, which effectively reduces the impact of adverse reactions on receptor-positive PBC patients, with higher safety and better feasibility.

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