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ORIGINAL RESEARCH

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Effects of zoledronic acid and exemestane combination therapy on immune function, sex hormones, bone markers, and clinical efficacy in hormone receptor-positive breast cancer patients

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Abstract

The effect of treatment by zoledronic acid combined with exemestane was explored pertaining to the immune function, sex hormones, bone markers, and clinical efficacy in hormone receptor-positive breast cancer patients. Eighty elderly patients with hormone receptor-positive breast cancer were selected as the study subjects who were clinically admitted from December 2016 to December 2021. The study and control groups had 40 cases each and were analyzed according to different treatment methods. The control group received exemestane treatment, while the study group was treated with a combination of zoledronic acid and exemestane. The immune functions, sex hormones, bone markers, clinical efficacy, adverse reactions, life quality scores, serum calcium, and vascular endothelial growth factor for the two groups were analyzed and compared. The cluster of differentiation (CD), E2, P and T levels were lower than those of the control after treatment, and the difference was statistically significant, $p < 0.05$. Similar effect was observed in β-Cross Laps, serum calcium levels and N-terminal propeptide of type 1precollagen (PINP) levels. Physiological and psychological scores were higher than the control after treatment, and difference was statistically significant, $p < 0.05$. The incidence of adverse reactions was 20.00% for the study group while 42.50% for control, and the difference was statistically significant, $p < 0.05$. We conclude that Zoledronic acid combined with exemestane in treating hormone receptor-positive breast cancer patients could improve clinical efficacy, immune function, bone metabolism, quality of life, regulate the sex hormones, and possess drug safety.

Keywords

Zoledronic acid; Exemestane; Breast cancer; Clinical efficacy; Immunologic function

1. Introduction

Breast cancer was a prevalent malignant tumor, and challenging for the patients as the early-stage clinical symptoms such as nipple discharge and breast lumps were not always visible. However, malignant tissues in the patient's body upon worsening of illness would continue to infiltrate and spread the tumor tissues and might manifest as distal metastasis. This could harm the patient's health and damage numerous tissues and organs in the body. Patients with estrogen- and progesterone-receptor-positive breast cancer had these receptors [1]. This group of breast cancer patients was in relatively high proportion among all breast cancers. The main clinical manifestations of such patients were hypercalcemia, painful sensations and the incidence of bone disease which affected the patients' quality of life. The prognosis of patients and prevention of bone illnesses were improved through timely and successful clinical therapies for these symptoms. Previous research [2] exhibited that radiotherapy and surgery were often used to treat these conditions, where radiotherapy alone could not adequately treat patients. Clinical investigations [3] discovered that the essential patient endocrine therapies were helpful in the patient's condition to regress. It was revealed [4] that exemestane as an anti-cancer drug was permanently bound to an aromatase active site, where it inactivated the enzyme in the patient's peripheral tissues to lower the estrogen levels, and aided in healing. Zoledronic acid as a diphosphonate had a strong affinity for mineralized bone which controlled the osteoclastic activity, lowered the bone resorption, minimized the risk of bone loss incurred by endocrine medications, and induced synergistic effect for tumor suppression [5, 6]. Purpose of this study was to investigate the effects of exemestane and zoledronic acid treatment on bone marker indexes, sex hormones, immune function, and clinical efficacy in elderly patients with hormone receptor-positive breast cancer, clinically admitted to our hospital between December 2016 and December 2021.

2. Data and methods

2.1 General data

Eight hormone receptor-positive elderly breast cancer patients clinically admitted between December 2016 and December 2021 were included in a comparative study. The study subjects were divided into study and control groups with 40 each according to various treatment approaches. The research group was treated with zoledronic acid and exemestane, while control group received only the exemestane treatment.

2.2 Selection criteria

(1) Inclusion criteria: (i) Diagnosis of breast cancer confirmed by clinical mammogram, breast ultrasound, pathology and immunological examination; (ii) signs of nipple invagination, breast lumps and distant metastasis; (iii) above 60 years old; and (iv) no contraindication to the drugs used in this study.

(2) Exclusion criteria: (i) those with multiple malignant tumors; (ii) recently received other treatments; and (iii) having combined psychiatric disorders.

2.3 Methods

2.3.1 Control group

The patients in the control group were treated with exemestane. They were given conventional radiotherapy, vitamin D, and exemestane tablets (Zhejiang Medicine Co., Ltd. Xinchang Pharmaceutical Factory, State Drug Quotient H20020004, Xinchang, China). The tablets had 25 mg/dose and were given orally after the meals once a day for 12 months.

2.3.2 Study group

Combined treatment of zoledronic acid with exemestane was given to this group. Exemestane was administered in the same way as the control group. Patients were statically injected once a month for 12 months with zoledronic acid (Renhe Yikang Group Co., Ltd., Guodianzhi H20233205, Shijiazhuang, China) dissolved in 100 mL saline solution.

2.4 Observation indexes

(1) Comparison of clinical data for the two groups.

(2) Comparison of immune function indexes ($CD3^+$, $CD4^+$, $CD4^+/CD8^+$) for the two groups.

(3) Comparison of sex hormone levels for the two groups (estradiol (E2), progesterone (P), testosterone (T)).

(4) Comparison of bone marker (β-collagen special sequence (β-Cross Laps), total bone type I procollagen amino-terminal extension peptide (PINP)) levels for the two groups.

(5) After treatment, the tumor tissue disappeared and no new tumor tissue was completely resolved in 1 month. Tumor tissue area after treatment was decreased by above 50% and lasted for 1 month as partial remission. The tumor tissue area after treatment did not change significantly and remained stable for 2 months. Patients with distant metastases were increased as the disease progressed.

(6) Comparison of adverse reaction incidence for the two groups.

(7) Survival quality for the two groups was compared. WHO QOL-BREF (The World Health Organisation Quality of life-Bref) scale was used to assess the survival quality before and 3 months after treatment by dividing it into physical and psychological with each item individually scored as 100.

(8) Serum calcium levels in both groups.

2.5 Statistical methods

Statistical data processing was conducted by SPSS (International Business Machines Corporation, Armonk, NY, USA) 22.0 software. Measurement data were expressed by ($\bar{x} \pm s$) and *t*-test, and count data by n (%). The χ^2 test was used for comparing the two groups, and the difference was considered statistically significant at $p < 0.05$.

3. Results

3.1 Comparison of clinical data for the two groups

There was no statistically significant difference between the baseline data of the two groups, $p > 0.05$ (Table 1).

3.2 Comparison of immune function indexes for the two groups

Immune function indexes before the treatment had no statistically significant difference in the two groups, $p > 0.05$; after the treatment, $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ levels were higher and $CD8^+$ levels were lower in the study group compared to those in the control, and the difference was statistically significant, $p < 0.05$ (Table 2 and Fig. 1).

3.3 Comparison of sex hormone indexes for the two groups (estradiol (E2), progesterone (P), and testosterone (T))

The sex hormone indexes of two groups before the treatment had no statistically significant difference, $p > 0.05$; E2, P and T values in the study group were lower than those in control after treatment, and the difference was statistically significant, $p < 0.05$ (Table 3 and Fig. 2).

3.4 Comparison of bone marker indexes for the two groups (β-Collagen special sequence (β-Cross Laps), total bone type I procollagen amino-terminal extension peptide (PINP))

The bone marker indexes of two groups before treatment had no statistically significant difference, $p > 0.05$; after treatment, the β-Cross Laps and PINP levels in study group were lower than those in control, and the difference was statistically significant, $p < 0.05$ (Table 4 and Fig. 3).

3.5 Comparison of incidence of adverse reactions for the two groups

The incidence of adverse reactions in the study group was 20.00% which was lower than in the control, *i.e.*, 42.50%. The difference was statistically significant, $p < 0.05$ (Table 5).

TABLE 1. Comparison of clinical data for the two groups.

Indicators	Study group (N = 40)	Control group (N = 40)	*t* value	*p* value
Age (yr) ($\bar{x} \pm s$)	68.28 ± 3.27	68.35 ± 3.25 (Age)		
Duration of disease (yr) ($\bar{x} \pm s$)	4.30 ± 0.46	4.28 ± 0.45 (yr)		
Education level (example)				
Secondary School and below	23	21	0.202	0.653
University and above	17	19		
Her-2 (cases)				
Negative	25	24	0.053	0.819
Positive	15	16		
Pathological TNM stage (cases)				
I	15	16		
II	15	14	0.067	0.967
III	10	10		
BMI (kg/m^2) ($\bar{x} \pm s$)	23.45 ± 2.16	23.51 ± 2.09	0.126	0.900

BMI: Body Mass Index; Pathological TNM: Pathological Tumor Node Metastasis.

TABLE 2. Comparison of immune function indexes for the two groups ($\bar{x} \pm s$).

Indicators	Study group (N = 40)	Control group (N = 40)	*t* value	*p* value
CD3$^+$ (%)				
Before treatment	48.32 ± 3.25	48.16 ± 3.19	0.222	0.825
After treatment	70.65 ± 6.54	64.35 ± 5.80	4.558	<0.001
t value	19.338	15.469	——	——
p value	<0.001	<0.001	——	——
CD4$^+$ (%)				
Before treatment	45.16 ± 2.31	45.86 ± 4.15	0.932	0.354
After treatment	28.49 ± 2.42	37.12 ± 3.52	10.158	<0.001
t value	31.514	10.158	——	——
p value	<0.001	<0.001	——	——
CD8$^+$ (%)				
Before treatment	28.31 ± 2.15	28.42 ± 2.26	0.223	0.824
After treatment	29.64 ± 2.34	31.82 ± 2.67	3.884	<0.001
t value	2.647	6.147	——	——
p value	0.010	<0.001	——	——
CD4$^+$/CD8$^+$				
Before treatment	1.12 ± 0.09	1.14 ± 0.08	1.050	0.297
After treatment	1.52 ± 0.12	1.35 ± 0.11	6.605	<0.001
t value	16.865	9.765	——	——
p value	<0.001	<0.001	——	——

CD: cluster of differentiation.

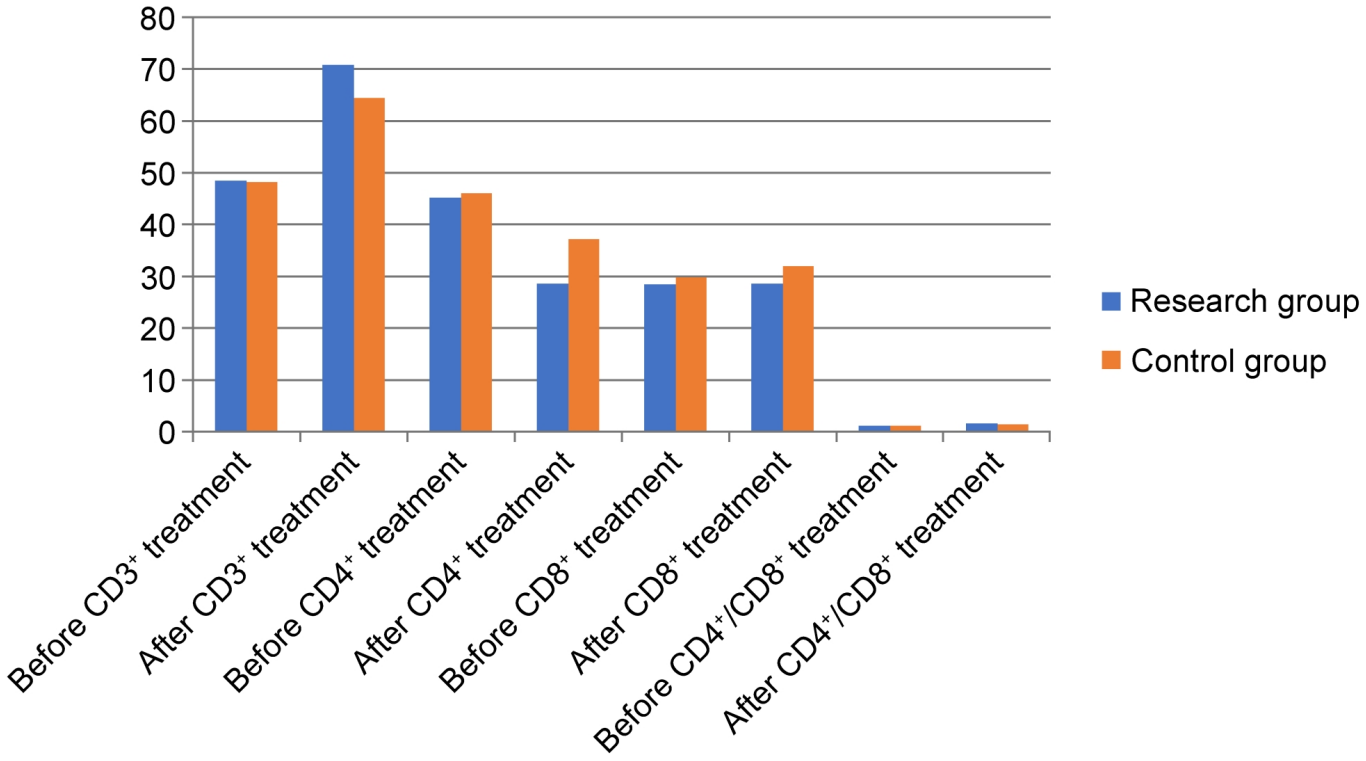

FIGURE 1. Comparison of immune function indicators for the two groups. CD: cluster of differentiation.

TABLE 3. Comparison of sex hormone indexes for the two groups (estradiol (E2), progesterone (P), and testosterone (T)) ($\bar{x} \pm s$).

Indicators	Study group (N = 40)	Control group (N = 40)	*t* value	*p* value
E2 (pg/mL)				
Before treatment	49.52 ± 3.87	49.26 ± 3.91	0.299	0.766
After treatment	28.69 ± 2.36	34.16 ± 3.21	8.683	<0.001
t value	29.064	18.878	——	——
p value	<0.001	<0.001	——	——
P (mg/mL)				
Before treatment	4.03 ± 0.31	4.08 ± 0.34	0.687	0.494
After treatment	3.41 ± 0.31	3.86 ± 0.35	6.087	<0.001
t value	8.944	2.851	——	——
p value	<0.001	0.006	——	——
T (ng/dL)				
Before treatment	38.25 ± 3.16	37.69 ± 3.21	0.786	0.434
After treatment	21.38 ± 1.19	26.57 ± 1.52	17.004	<0.001
t value	31.598	19.802	——	——
p value	<0.001	<0.001	——	——

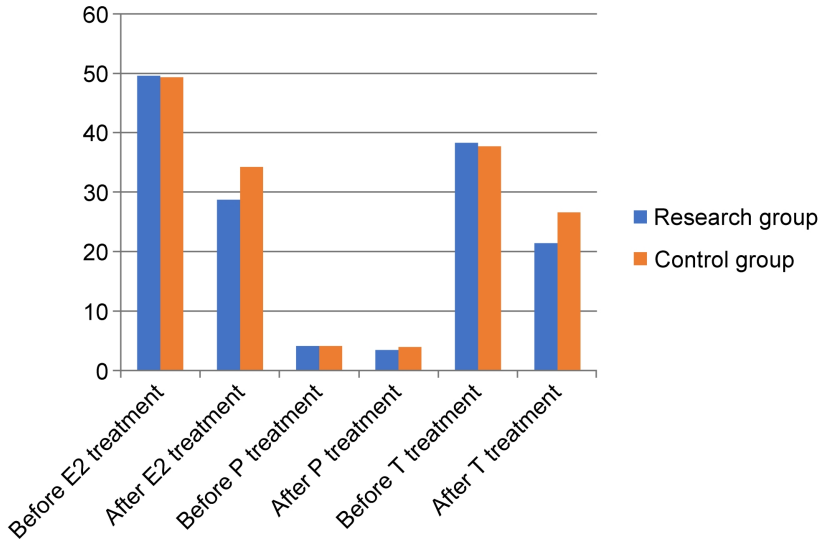

FIGURE 2. Comparison of sex hormone indexes for the two groups. E2: estradiol; P: progesterone; T: testosterone.

TABLE 4. Comparison of bone marker indexes for the two groups (β-Collagen special sequence (β-Cross Laps), total bone type I procollagen amino-terminal extension peptide (PINP)) ($\bar{x} \pm s$).

Indicators	Study group (N = 40)	Control group (N = 40)	*t* value	*p* value
β-Cross Laps (ng/L)				
Before treatment	841.36 ± 52.14	836.54 ± 51.06	0.418	0.677
After treatment	415.87 ± 39.23	460.25 ± 37.21	5.191	<0.001
t value	41.242	37.668	——	——
p value	<0.001	<0.001	——	——
PINP (μg/L)				
Before treatment	87.64 ± 7.21	86.95 ± 7.53	0.437	0.663
After treatment	40.94 ± 3.52	45.98 ± 3.87	6.093	<0.001
t value	36.812	30.606	——	——
p value	<0.001	<0.001	——	——

PINP: type I procollagen amino-terminal extension peptide.

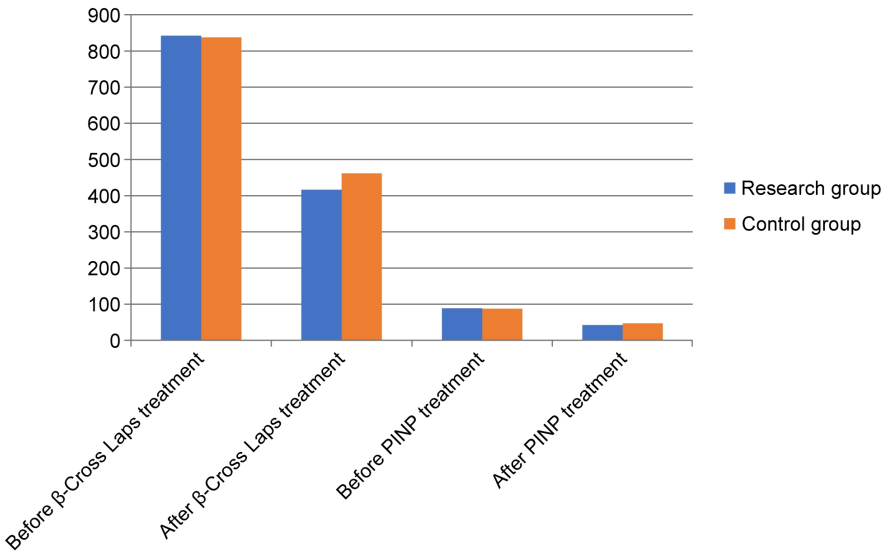

FIGURE 3. Comparison of bone markers for the two groups. PINP: type I procollagen amino-terminal extension peptide.

TABLE 5. Comparison of adverse reactions for the two groups n (%).

Adverse effects	Study group (N = 40)	Control group (N = 40)	χ^2 value	p value
Decreased platelets	3 (7.50)	6 (15.00)		
Nausea and vomiting	3 (7.50)	7 (17.50)		
Anemia	2 (5.00)	4 (10.00)		
Total adverse reaction rate	8 (20.00)	17 (42.50)	4.712	0.029

3.6 Comparison of survival quality for the two groups

The difference of physiological and psychological scores for the two groups before treatment was not statistically significant, $p > 0.05$; 3 months after the treatment, physiological and psychological scores of study group were higher than of control, and the difference was statistically significant, $p < 0.05$ (Table 6 and Fig. 4).

3.7 Comparison of serum calcium levels for the two groups

The serum calcium levels of the two groups before the treatment had no statistically significant difference, $p > 0.05$; after the treatment, serum calcium levels of the study group were lower than of the control, and the difference was statistically significant, $p < 0.05$ (Table 7 and Fig. 5).

4. Discussion

The prevalence of this illness was consistently on the rise with worsening of living conditions and quickening the life pace. Radiotherapy was the primary clinical treatment for this illness having an anti-cancer impact that prolonged the patients' survival times. However, patients of this disease stage often experienced bone pain and had poor prognosis. The current clinical treatment for hormone receptor-positive breast cancer patients is based on letrozole therapy [7, 8]. This drug in the process of tumor suppression and hormone regulation had adverse effects on immune function and bone health of patients which hampered the patients' life quality [9, 10]. In this study, zoledronic acid and exemestane were used to clinically treat hormone-receptor-positive breast cancer patients. The study aimed to evaluate a modified therapy regimen for boosting patients' immune systems and increasing bone metabolism, where positive clinical outcomes were obtained.

Results of this study depicted that $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ levels were higher and $CD8^+$ levels were lower after the treatment in the study group compared to the control ($p < 0.05$), suggesting that combination therapy improved the immune function. Exemestane combined with zoledronic acid stimulated the activation and proliferation of T lymphocytes, activated the relevant signaling channels, prevented inflammation, controlled the body's immune response *in vivo*, and aided in patients' recovery while inhibiting the cancer cells' proliferation. This could be attributed to the blocking of androstenedione as secreted by the adrenal gland and converted to estrogen, which inhibited the estrogen and blocked cancer cell proliferation as well as regulated the vascular endothelial factor levels [11–13].

Results exhibited that serum calcium after the treatment was lower in the study group compared to the control ($p < 0.05$). Serum calcium levels could thus be altered with this combination therapy. Zoledronic acid being a bisphosphonate drug inhibited the osteoclasts-producing precursor cells, prevented the osteoclasts from lysing bone trabeculae, prevented the tumor cells from adhering to bone matrix, prevented tumor lesions from tissue-mediated osteolytic lesions, and prevented the increase of serum calcium [14–16].

Findings indicated that Cross Laps and PINP levels after the treatment were lower in the study group than in the control ($p < 0.05$), and E2, P and T were also lower. The combination therapy might thus control estrogen levels and bone metabolism. This was because zoledronic acid controlled the osteoclast activity and prevented bone trabeculae from being ablated. Moreover, the medication inhibited the release of bone matrix growth factor, blocked the adhesion of tumor tissue onto the bone matrix, and prevented bone resorption which in turn prevented the tumor tissue-induced bone lesions, lowered the sex hormone levels, and regulated bone marker levels [15–17].

The physiological and psychological scores of the study group were higher than those of the control after 1 and 3 months of treatment. The incidence of adverse reactions in the study group was 20.00% which was lower than that of the control, 42.50% ($p < 0.05$). The combination therapy thus improved the survival quality of patients along with medication safety. Overall, zoledronic acid had an efficient anti-tumor effect. It controlled the human epidermal growth factor receptor complex kinase tissue activity. It formed the abrogating effect on cancer cells. It blocked the spread of cancer cells or the occurrence of distant metastasis, which induced cancer cell decay and improved clinical efficacy [18–20].

5. Conclusions

The zoledronic acid and exemestane combination therapy for hormone receptor-positive breast cancer patients enhanced the clinical efficacy and immune function, and improved bone metabolism and survival quality. It regulated sex hormones, with overall medication safety. However, there were some limitations of this study, such as the small number of samples selected which might create selective bias, and the short follow-up period of treatment which hindered systematic assessment of patients' future survival. In the future, the source of cases should be enriched to validate the treatment efficacy in a broader scope and extend the follow-up period to verify the long-term efficacy of this treatment.

TABLE 6. Comparison of survival quality for the two groups ($(\bar{x} \pm s)$, Scores).

Indicators	Study group (N = 40)	Control group (N = 40)	*t* value	*p* value
Physiology				
Before treatment	61.53 ± 6.25	61.87 ± 5.97	0.249	0.804
3 months after treatment	73.56 ± 6.84	65.32 ± 6.28	5.612	<0.001
t value	8.212	2.518	——	——
p value	<0.001	0.014	——	——
Psychological				
Before treatment	60.65 ± 6.82	60.25 ± 5.98	0.279	0.781
3 months after treatment	72.56 ± 6.91	64.25 ± 5.96	5.760	<0.001
t value	7.759	2.996	——	——
p value	<0.001	0.004	——	——

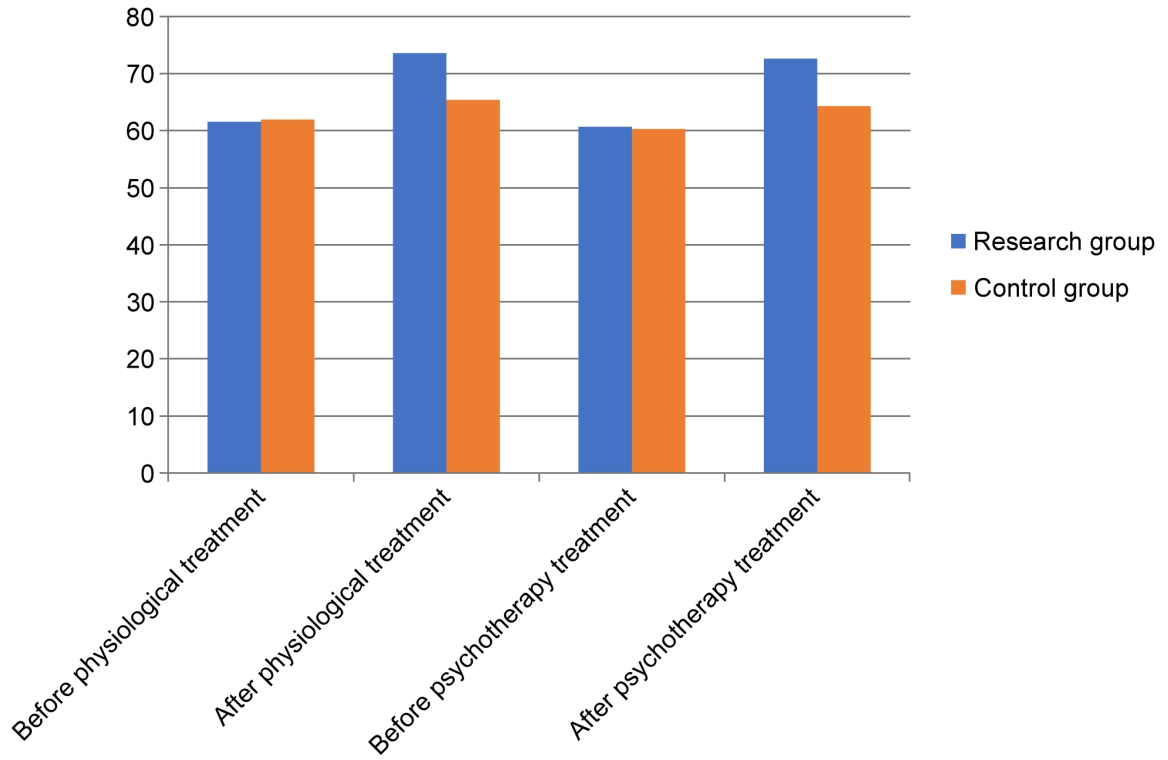

FIGURE 4. Comparison of life quality for the two groups.

TABLE 7. Comparison of serum calcium for the two groups ($\bar{x} \pm s$).

Indicators	Study group (N = 40)	Control group (N = 40)	*t* value	*p* value
Serum calcium (mmol/L)				
Before treatment	3.61 ± 0.28	3.59 ± 0.26	0.331	0.742
After treatment	2.51 ± 0.16	2.92 ± 0.26	8.494	<0.001
t value	21.573	11.524	——	——
p value	<0.001	<0.001	——	——

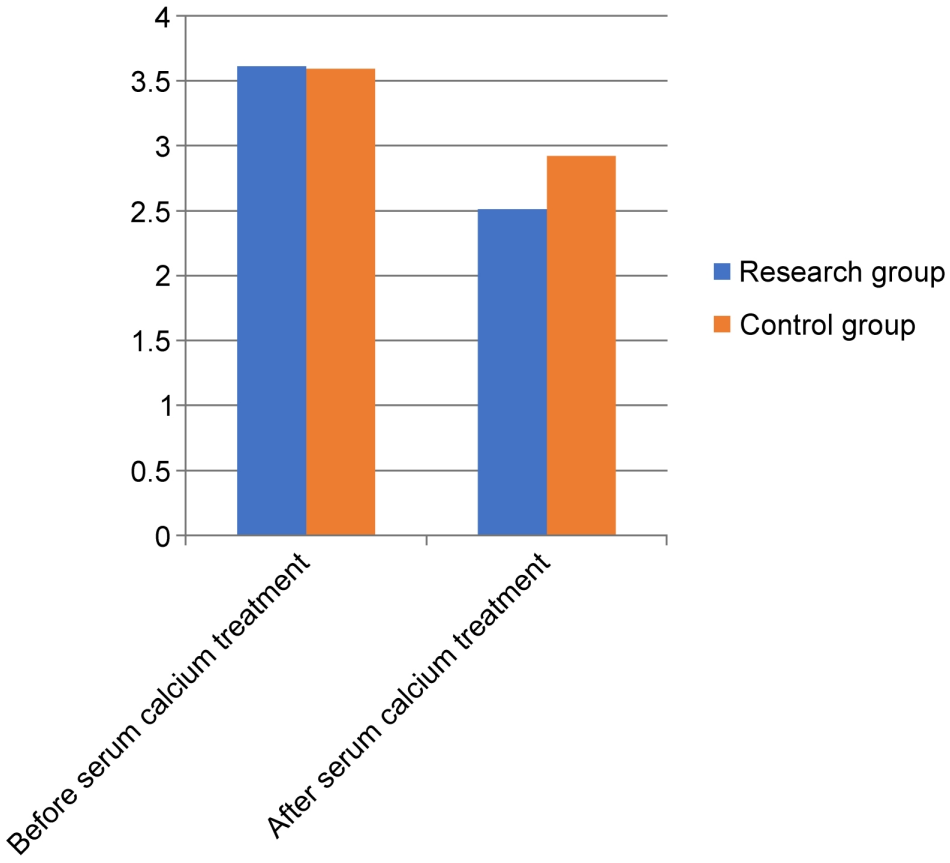

FIGURE 5. Comparison of serum calcium levels for the two groups.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

RPZ, CC and LLZ—designed the study and carried it out; supervised the data collection, analyzed the data, interpreted the data, prepared the manuscript for publication, and reviewed the manuscript draft. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of The Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University (Approval no. KY-P-2019-007-01). Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Turner NC, Swift C, Kilburn L, Fribbens C, Beaney M, Garcia-Murillas I, Budzar AU, *et al*. *ESR1* mutations and overall survival on fulvestrant versus exemestane in advanced hormone receptor-positive breast cancer: a combined analysis of the phase III SoFEA and EFECT trials. Clinical Cancer Research. 2020; 26: 5172–5177.

[2] Bardia A, Hurvitz SA, DeMichele A, Clark AS, Zelnak A, Yardley DA, *et al*. Phase I/II trial of Exemestane, Ribociclib, and Everolimus in women with $HR^{+}/HER2^{-}$ advanced breast cancer after progression on CDK4/6 inhibitors (TRINITI-1). Clinical Cancer Research. 2021; 27: 4177–4185.

[3] Pagani O, Walley BA, Fleming GF, Colleoni M, Láng I, Gomez HL, *et al*. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer: long-term follow-up of the combined TEXT and SOFT trials. Journal of Clinical Oncology. 2023; 41: 1376–1382.

[4] Makhlin I, McAndrew NP, Wileyto EP, Clark AS, Holmes R, Bottalico LN, *et al*. Ruxolitinib and exemestane for estrogen receptor-positive, aromatase inhibitor resistant advanced breast cancer. NPJ Breast Cancer. 2022; 8: 122.

[5] Ishikawa T. Differences between zoledronic acid and denosumab for breast cancer treatment. Journal of Bone and Mineral Metabolism. 2023; 41: 301–306.

[6] Sheweita SA, Ammar RG, Sabra SA, Sultan AS. Letrozole and zoledronic acid changed signalling pathways involved in the apoptosis of breast

cancer cells. Journal of Taibah University Medical Sciences. 2021; 16: 112–120.

[7] Sorscher S. Duration and dose of adjuvant zoledronic acid for treatment of early breast cancer. JAMA Oncology. 2022; 8: 171.

[8] Wang Q, Guo G, Ruan Z, Cao H, Guo Y, Bai L, *et al*. Safety and efficacy of long-term zoledronic acid in advanced breast cancer with bone metastasis in South China. Journal of Oncology. 2020; 2020: 5670601.

[9] Rahimian L, Kalantari Khandani B, Nemati M, Hoseini-Shahrestanak S, Aminizadeh N, Jafarzadeh A. Reduced expression of natural killer cell-related activating receptors by peripheral blood mononuclear cells from patients with breast cancer and their improvement by zoledronic acid. Asian Pacific Journal of Cancer Prevention. 2022; 23: 1661–1669.

[10] Friedl TWP, Janni W, Rack B. Duration and dose of adjuvant zoledronic acid for treatment of early breast cancer—reply. JAMA Oncology. 2022; 8: 171–172.

[11] Kim JW, Lee S, Kim HS, Choi YJ, Yoo J, Park KU, *et al*. Prognostic effects of cytokine levels on patients treated with taxane and zoledronic acid for metastatic breast cancer in bone (BEAT-ZO) (KCSG BR 10-13). Cytokine. 2021; 142: 155487.

[12] Yamada K, Kaise H, Taguchi T, Horiguchi J, Takao S, Suzuki M, *et al*. Strontium-89 plus zoledronic acid versus zoledronic acid for patients with painful bone metastatic breast cancer. Journal of Bone and Mineral Metabolism. 2022; 40: 998–1006.

[13] Vidula N, Greenberg S, Petrillo L, Hwang J, Melisko M, Goga A, *et al*. Evaluation of disseminated tumor cells and circulating tumor cells in patients with breast cancer receiving adjuvant zoledronic acid. NPJ Breast Cancer. 2021; 7: 113.

[14] Buch-Larsen K, Jørgensen NR, Jensen LT, Andersson M, Schwarz P. Denosumab *vs.* zoledronic acid treatment in post-menopausal breast cancer: a 2-year prospective observational study. Scandinavian Journal of Clinical and Laboratory Investigation. 2021; 81: 425–431.

[15] Crocamo S, Binato R, Dos Santos EC, de Paula B, Abdelhay E. Translational results of Zo-NAnTax: a phase II trial of neoadjuvant zoledronic acid in HER2-positive breast cancer. International Journal of Molecular Sciences. 2022; 23: 15515.

[16] Jallouk AP, Paravastu S, Weilbaecher K, Aft RL. Long-term outcome of (neo)adjuvant zoledronic acid therapy in locally advanced breast cancer. Breast Cancer Research and Treatment. 2021; 187: 135–144.

[17] Huang X, Liu Y, Lin S, Wang H, Deng Y, Rao X, *et al*. Adjuvant zoledronic acid therapy for postmenopausal women with early breast cancer in China: a cost-effectiveness analysis. International Journal for Quality in Health Care. 2023; 35: mzad016.

[18] Liu M, Qian S, Wu J, Xiao J, Zeng X. The effects of neoadjuvant zoledronic acid in breast cancer patients: a meta-analysis of randomized controlled trials. Asian Journal of Surgery. 2023; 46: 4124–4130.

[19] Matsuura K, Saeki T, Takahashi T, Torigoe T, Watarai K, Osaki A, *et al*. Bilateral femoral head osteonecrosis in a patient with metastatic breast cancer receiving long-term zoledronic acid treatment: a case report. Molecular and Clinical Oncology. 2021; 15: 166.

[20] Chacko G, Kota S, Kumar S, Ohri N, Omene C, Ganesan S, *et al*. Uveitis, is a rare but important complication of adjuvant zoledronic acid for early-stage breast cancer. Anti-Cancer Drugs. 2023; 34: 592–594.

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