Research Article

Efficacy, Safety, and Prognosis of Sequential Therapy with Tamoxifen and Letrozole versus Letrozole Monotherapy for Breast Carcinoma

Xinli Lu¹ and Cheng Qian²

¹Pharmacy Intravenous Admixture Services, the First People’s Hospital of Ningyang County, Tai’an 271400, Shandong, China
²Department of Thyroid and Breast Surgery, Zhuji People’s Hospital of Zhejiang Province, Zhejiang 311800, China

Correspondence should be addressed to Cheng Qian; qiancheng1978abc@163.com

Received 26 January 2022; Revised 1 March 2022; Accepted 12 March 2022; Published 14 April 2022

Academic Editor: Min Tang

Copyright © 2022 Xinli Lu and Cheng Qian. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Objective. To explore the efficacy, safety, and patient prognosis of letrozole (LTZ) alone or in sequence with tamoxifen (TAM) for the treatment of breast carcinoma (BC).

Methods. In this retrospective study, 150 patients with BC who received treatment in the First People’s Hospital of Ningyang County between January 2012 and January 2017 were selected. According to different treatment methods, 99 cases receiving sequential therapy with TAM and LTZ were included in the research group, and the remaining 51 patients receiving LTZ monotherapy were selected as the control group. The efficacy, safety, survival rate, recurrence rate, and blood lipid indices (total cholesterol, TC; triglyceride, TG; high-density lipoprotein cholesterol, HDL-C; and low-density lipoprotein cholesterol, LDL-C) of the two groups were observed and compared.

Results. The overall response rate of the research group was statistically higher than that of the control group, and the incidence of adverse reactions was significantly lower. No evident difference was observed in 1-, 3-, or 5-year survival rates between the two groups, while the 3-5-year recurrence rate was obviously lower, and the improvement of blood lipid indices was significantly better in the research group compared with the control group.

Conclusion. LTZ alone or in sequence with TAM is effective and safe for the treatment of BC, which can significantly improve the prognosis and blood lipid indices of BC patients.

1. Introduction

Breast carcinoma (BC) is a genetically heterogeneous fatal disease and a common female cancer [1]. According to epidemiological data, there are approximately 2.3 million new cases of BC and 685,000 deaths worldwide [2]. With the constant optimization of BC screening methods and treatments in recent years, its recurrence rate and mortality rate have been declining, with a 5-year overall survival rate even over 90% in some countries [3]. However, once BC has metastasized, the average 5-year survival rate is as low as 22%, with certain risk of recurrence [4]. Recurrence or posttreatment complications are the main causes of morbidity and mortality in BC patients [5, 6]. Therefore, analyzing the clinical effects of treatment methods from the perspective of efficacy, safety, and patient prognosis is of great significance for reducing the mortality and recurrence rate of BC, which can also provide new clinical references for BC treatment.

This study mainly analyzes the clinical therapeutic effect of sequential therapy with tamoxifen (TAM) and letrozole (LTZ) versus LTZ monotherapy in the treatment of BC. It is shown that the tumor tissue of most BC patients is estrogen-dependent, and inhibiting estrogen stimulation of tumors can help to curb cancer progression [7]. Both TAM and LTZ are common antiestrogen drugs in clinic [8]. Among them, TAM is an antitumor drug, which is used as an estrogen receptor regulator in adjuvant endocrine therapy for hormone-dependent BC [9, 10]. LTZ, a common endocrine drug, is an aromatase inhibitor that blocks estrogen synthesis by inhibiting the final step of the estrogen biosynthesis pathway [11]. Since the effect of LTZ monotherapy...
is not satisfactory, it is often used in combination with other drugs or in sequence with TAM to improve the efficacy of BC treatment [8, 12]. Previous studies have shown that LTZ in sequence with TAM can increase the efficacy and safety of patients with early-stage BC to a certain extent [13]. Herein, we will analyze the effects of the two treatment methods on the clinical effect of BC patients from a more multidimensional perspective, aiming at providing a more comprehensive reference for clinical treatment of BC.

2. Materials and Methods

2.1. General Data. This is a retrospective study. A total of 150 BC patients admitted to the First People’s Hospital of Ningyang County from January 2012 to January 2017 were selected and grouped according to treatment methods. Among them, 99 patients treated with sequential therapy with TAM and LTZ were included in the research group, and 51 patients treated with LTZ monotherapy were assigned to the control group. Inclusion criteria are as follows: diagnosis of BC, nonspecial invasive carcinoma, no history of contraindications to the study medication, normal cognitive and communication skills, and nonlactating and nonpregnant patients. Exclusion criteria are as follows: malignant tumor(s), other breast diseases, endocrine diseases or infectious diseases, prior treatment, and use of estrogen drugs in the past three months. This study was approved by the Ethics Committee of the First People’s Hospital of Ningyang County, and all the subjects provided informed consent.

2.2. Treatment Methods. Patients in the control group were given LTZ (Beijing Kaishiyuan Biotechnology Co., Ltd., SC05834), per os, 2.5 mg once a day, for 5 years. The research group was treated with LTZ sequentially following initial TAM therapy. Subjects received TAM citrate tablets (Hengyang Jinyi Biotechnology Co., Ltd., 54965-24-1) 10 mg orally twice daily for 2 years, followed by LTZ for 3 years as described above.

2.3. Efficacy Evaluation. Complete response (CR): all lesions disappeared for at least one month, and the remission time increased with the treatment time. Partial response (PR): the lesion basically disappeared or shrank by at least 50%, and this state was maintained for at least one month. Stable disease (SD): the lesion changed little. Progressive disease (PD): the lesion progressed with distant metastasis or lesion increase by at least 25%. The overall response rate (ORR) was the sum of CR rate and PR rate.

2.4. Outcome Measures. Safety. The incidence rates of nausea and vomiting, hyperlipidemia, thromboembolism, and muscle and joint pain were recorded in both groups, and the total incidence of adverse reactions was calculated.

Prognosis. The 1-year, 3-year, and 5-year survival rates as well as the 1-year, 1-3-year, and 3-5-year recurrence rates, were evaluated in both groups. The subjects were followed up every three months through telephone interviews, visits, and pathological data inquiries.

Blood lipid indices. Total cholesterol (TC) and triglyceride (TG), as well as high- and low-density lipoprotein cholesterol (HDL-C/LDL-C), were detected using a blood lipid analyzer (Shanghai Xinfan Biotechnology Co., Ltd., ZDSJ082).

2.5. Statistical Analysis. SPSS 17.0 (IBM SPSS, Madrid, Spain) and GraphPad Prism 6 (GraphPad Software, San Diego, California, USA) were used for data analysis and image rendering, respectively. Number of cases/percentages (n/%) was used to represent the counting data, and the comparison was performed by the Chi-square test. The measurement data were described as mean ± SEM, and the statistical methods for intergroup and intragroup comparisons were independent samples t-test and paired t-test, respectively. The significance level was set at $P < 0.05$.

3. Results

3.1. The General Data of the Two Groups Were Comparable. The research group and the control group showed no significant difference in general data such as age, average age, tumor staging, histological type, operation mode, drinking history, smoking history, and marital status ($P < 0.05$) (Table 1).

3.2. The Efficacy of the Research Group Was Significantly Higher Than That of the Control Group. The cases of CR, PR, SD, and PD in the control group were 7, 13, 17, and 14, respectively, while the corresponding cases in the research group were 30, 27, 19, and 23. The ORR of the research group was 57.57%, which was higher than that of the control group (39.22%), with statistical significance ($P < 0.05$) (Table 2).

3.3. The Incidence of Adverse Reactions in the Research Group Was Significantly Lower Than That in the Control Group. The cases of nausea and vomiting, hyperlipidemia, thromboembolism, and muscle and joint pain in the control group were 8, 6, 5, and 4, respectively, and the corresponding cases in the research group were 5, 3, 2, and 0. The total incidence of adverse reactions was 10.10% in the research group and 45.09% in the control group, with statistical significance between the two groups ($P < 0.05$) (Table 3).

3.4. There Was No Significant Difference in Patient Prognosis between the Research Group and the Control Group. In terms of survival, the 1-year, 3-year, and 5-year survival rates of the research group were not significantly different from those of the control group ($P > 0.05$). As to recurrence, the 1-year and 1-3-year recurrence rates showed no significant difference between the two groups ($P > 0.05$). However, the 3-5-year recurrence rate was lower in the research group compared with the control group, with statistical significance ($P < 0.05$) (Table 4).

3.5. The Blood Lipid Indices of the Research Group Were Significantly Better than Those of the Control Group after Treatment. We also compared serum lipids between the
two groups, and the data showed no significant difference in lipid indices before treatment ($P > 0.05$). In the control group, the four blood lipid indices (TC, TG, HDL-C, and LDL-C) did not change significantly before and after treatment ($P > 0.05$). However, after treatment, TC, TG, and LDL-C were lower and HDL-C was higher in the research group compared with the control group, with statistically significant differences ($P < 0.05$) (Figure 1).

4. Discussion

BC is a common gynecological malignant tumor, seriously threatening women's physical and mental health and even life [14]. The pathogenesis of BC is complex and has not been thoroughly clarified [15]. However, most BCs are identified as estrogen-dependent tumors, and the treatment breakthrough of this disease is to inhibit the stimulation of
The two drugs used in this study, TAM and LTZ, have varying degrees of resistance to estrogen. Among them, TAM can inhibit the binding of normal progesterone, estrogen, and receptors in the body by binding to the epidermal hormone receptors of BC cells, thus preventing tumor growth, while LTZ can restrain the growth of estrogen-dependent BC cells via inhibiting aromatase activity.

In this study, 99 patients treated with LTZ sequentially following initial TAM therapy were set as the research group, and 51 patients treated with LTZ monotherapy were taken as the controls. The analysis of clinical efficacy revealed a statistically higher ORR of the research group compared with the control group (57.57% vs. 39.22%). This suggests that the efficacy of the sequential therapy with LTZ and TAM has a significantly higher efficacy than LTZ monotherapy, which may be related to the negative impact of drug resistance on efficacy under monotherapy. It has also been pointed out that TAM resistance, the main obstacle to BC treatment, can be overcome by blocking the production of estrogen, thus improving the clinical effect.

In terms of safety, the two groups of patients in this study mainly had complications such as nausea and vomiting, hyperlipidemia, and thromboembolism, which were similar to some previous studies. In addition, this research identified a statistically lower incidence of adverse reactions in the research group compared with the control group (10.10% vs. 45.09%), indicating that LTZ in sequence with TAM improves patient safety.

In the study of Regan et al., it was pointed out that sequential therapy of TAM and LTZ did not significantly improve the prognosis of BC patients compared with LTZ alone, but had a beneficial effect on the recurrence risk and treatment tolerance of patients. Finally, we analyzed the blood lipid indices and found that the blood lipid indices of the research group receiving sequential drug may be beneficial to activate the pharmacological activity of TAM in patients, thus improving the ORR. In terms of safety, the two groups of patients in this study mainly had complications such as nausea and vomiting, hyperlipidemia, and thromboembolism, which were similar to some previous studies.

### Table 4: Prognosis of patients in two groups (n/%).

| Categories          | Control group (n = 51) | Research group (n = 99) | $\chi^2$ value | $P$ value |
|---------------------|------------------------|-------------------------|----------------|-----------|
| 1-year survival rate| 47 (92.16)             | 94 (94.95)              | 0.042          | 0.838     |
| 3-year survival rate| 44 (86.27)             | 85 (85.86)              | 0.005          | 0.945     |
| 5-year survival rate| 37 (72.55)             | 79 (79.80)              | 1.009          | 0.315     |
| 1-year recurrence rate | 3 (5.88)               | 4 (4.04)                | 0.257          | 0.612     |
| 1-3-year recurrence rate | 7 (13.73)             | 8 (8.08)                | 0.275          | 1.192     |
| 3-5-year recurrence rate | 16 (31.37)             | 11 (11.11)              | 9.362          | 0.002     |

### Figure 1: Blood lipid indices of two groups of patients.

(a) Comparison of TC before and after treatment between the two groups
(b) Comparison of TG before and after treatment between the two groups
(c) Comparison of HDL-C before and after treatment between the two groups
(d) Comparison of LDL-C before and after treatment between the two groups

**Note:** **P** < 0.01.
therapy with TAM and LTZ were significantly better, suggesting that the sequential treatment had some beneficial effects on improving the blood lipid of patients. Del Mastro et al. [25] also confirmed that sequential therapy with TAM and LTZ was the best standard treatment strategy for post-menopausal hormone-receptor-positive BC patients, which is similar to the results of our study.

The novelty of this study is to confirm that the sequential therapy with TAM and LTZ has a better clinical effect in the treatment of BC, as it can significantly improve the efficacy, safety, prognosis, and lipid indices of patients, which provides a more detailed clinical reference for the management of BC patients. However, there is still room for improvement in this study. First, we can increase the clinical sample size to improve the accuracy of experimental results. Second, inflammatory factors, oxidative stress, and other indicators can be detected to further supplement the effects of the two drug therapies on these indicators. Third, the analysis of risk factors affecting recurrence of BC patients can be supplemented to verify whether there is a certain correlation between medication pattern and recurrence of patients. We will conduct supplementary studies from the above perspectives in the future.

5. Conclusion

To sum up, either LTZ alone or in sequence with TAM for BC can not only improve the efficacy and safety of patients but also help to improve their prognosis and lipid indices, providing new insights into the mode of medication for patients with BC.

Data Availability

The labeled dataset used to support the findings of this study is available from the corresponding author upon request.

Conflicts of Interest

The authors declare no competing interests.

References

[1] L. Tian, M. J. Truong, C. Lagadec et al., "S-ship promoter expression identifies mouse mammary cancer stem cells," Stem Cell Reports, vol. 13, no. 1, pp. 10–20, 2019.
[2] S. Lei, R. Zheng, S. Zhang et al., "Global patterns of breast cancer incidence and mortality: a population-based cancer registry data analysis from 2000 to 2020," Cancer Communications, vol. 41, no. 11, pp. 1183–1194, 2021.
[3] J. Ding, Y. Guo, X. Jiang, K. Li, W. Fu, and Y. Cao, "Concomitant fulvestrant with reirradiation for unrectable locoregional recurrent estrogen receptor positive (er+ ) breast cancer: a case report and narrative review," Medicine (Baltimore), vol. 99, no. 30, article e21344, 2020.
[4] E. M. Schunkert, W. Zhao, and K. Zanker, "Breast cancer recurrence risk assessment: is non-invasive monitoring an option?", Biomedicine Hub, vol. 3, no. 3, pp. 1–17, 2018.
[5] Y. Wang, J. Li, L. Dai, J. Zheng, Z. Yi, and L. Chen, "Mir-17-5p may serve as a novel predictor for breast cancer recurrence," Cancer Biomarkers, vol. 22, no. 4, pp. 721–726, 2018.
[6] M. Ewertz, L. H. Land, S. O. Dalton, D. Cronin-Fenton, and M. B. Jensen, "Influence of specific comorbidities on survival after early-stage breast cancer," Acta Oncologica, vol. 57, no. 1, pp. 129–134, 2018.
[7] Y. El-Ahmad, M. Tabart, F. Halley et al., "Discovery of 6-(2,4-sichlorophenyl)-5-{[4-(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]}oxyphenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (SAR439859), a potent and selective estrogen receptor degrader (SERD) for the treatment of estrogen-receptor-positive breast cancer," Journal of Medicinal Chemistry, vol. 63, no. 2, pp. 512–528, 2020.
[8] J. Letourneau, F. Juarez-Hernandez, K. Wald et al., "Concomitant tamoxifen or letrozole for optimal oocyte yield during fertility preservation for breast cancer: the tamoxifen or letrozole in estrogen sensitive tumors (tales) randomized clinical trial," Journal of Assisted Reproduction and Genetics, vol. 38, no. 9, pp. 2455–2463, 2021.
[9] R. Mofarrah, R. Mofarrah, B. Kranke et al., "First report of tamoxifen-induced baboon syndrome," Journal of Cosmetic Dermatology, vol. 20, no. 8, pp. 2574–2578, 2021.
[10] Y. Wang, W. Yue, H. Lang, X. Ding, X. Chen, and H. Chen, "Resuming sensitivity of tamoxifen-resistant breast cancer cells to tamoxifen by tetrandrine," Integrative Cancer Therapies, vol. 20, 2021.
[11] A. M. Yang, N. Cui, Y. F. Sun, and G. M. Hao, "Letrozole for female infertility," Frontiers in Endocrinology, vol. 12, article 676133, 2021.
[12] A. DeMichele, M. Cristofanilli, A. Brufsky et al., "Comparative effectiveness of first-line palbociclib plus letrozole versus letrozole alone for hr+/her2- metastatic breast cancer in us real-world clinical practice," Breast Cancer Research, vol. 23, no. 1, p. 37, 2021.
[13] A. G.-H. Mouridsen, A. Goldhirsch, B. Thurlimann et al., "Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer," The New England Journal of Medicine, vol. 361, no. 8, pp. 766–776, 2009.
[14] H. Chen, Y. Zhang, X. Cao, and P. Mou, "Mir-27a facilitates breast cancer progression via GSK-3β," Technology in Cancer Research & Treatment, vol. 19, 2020.
[15] H. L. Zhang, X. X. Wang, and F. Zhang, "Correlations of the mir-330 expression with the pathogenesis and prognosis of breast cancer," European Review for Medical and Pharmacological Sciences, vol. 23, no. 4, pp. 1584–1590, 2019.
[16] C. Wang, F. Bai, L. H. Zhang, A. Scott, E. Li, and X. H. Pei, "Estrogen promotes estrogen receptor negative brcal-deficient tumor initiation and progression," Breast Cancer Research, vol. 20, no. 1, p. 74, 2018.
[17] B. J. Long, D. Jelovac, V. Handratta et al., "Therapeutic strategies using the aromatase inhibitor letrozole and tamoxifen in a breast cancer model," Journal of Assisted Reproduction and Genetics, vol. 16, no. 1, pp. 74–86, 2019.
[18] N. Ijichi, T. Shigekawa, K. Ikeda et al., "Association of double-positive foxa1 and foxp1 immunoreactivities with favorable prognosis of tamoxifen-treated breast cancer patients," Horm Cancer, vol. 3, no. 4, pp. 147–159, 2012.
[19] Y. Zhang, H. Su, M. Rahimi, R. Tochihara, and C. Tang, "Egfrviii-induced estrogen-independence, tamoxifen-resistance phenotype correlates with PgR expression and modulation of...
apoptotic molecules in breast cancer,” *International Journal of Cancer*, vol. 125, no. 9, pp. 2021–2028, 2009.

[20] Y. Wang, S. Li, L. Zhu et al., “Letrozole improves the sensitivity of breast cancer cells overexpressing aromatase to cisplatin via down-regulation of fen1,” *Clinical & Translational Oncology*, vol. 21, no. 8, pp. 1026–1033, 2019.

[21] S. Catalano, C. Giordano, S. Panza et al., “Tamoxifen through GPER upregulates aromatase expression: a novel mechanism sustaining tamoxifen-resistant breast cancer cell growth,” *Breast Cancer Research and Treatment*, vol. 146, no. 2, pp. 273–285, 2014.

[22] S. Tang, Q. Zhang, X. Tang et al., “Long-term comparisons of the efficacy, safety, and pregnancy outcomes of adjuvant tamoxifen plus ovarian function suppression in premenopausal Han and Zhuang Chinese patients with hormone receptor-positive early breast cancer,” *The Journal of International Medical Research*, vol. 47, no. 2, pp. 641–652, 2019.

[23] H. Eggemann, A. L. Bernreiter, M. Reinisch et al., “Tamoxifen treatment for male breast cancer and risk of thromboembolism: prospective cohort analysis,” *British Journal of Cancer*, vol. 120, no. 3, pp. 301–305, 2019.

[24] M. M. Regan, P. Neven, A. Giobbie-Hurder et al., “1-98 Collaborative Group; International Breast Cancer Study Group (IBCSG). Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8-1 years median follow-up,” *The Lancet Oncology*, vol. 12, no. 12, pp. 1101–1108, 2011.

[25] L. Del Mastro, M. Mansutti, G. Bisagni et al., “Gruppo Italiano Mammella investigators. Extended therapy with letrozole as adjuvant treatment of postmenopausal patients with early-stage breast cancer: a multicentre, open-label, randomised, phase 3 trial,” *The Lancet Oncology*, vol. 22, no. 10, pp. 1458–1467, 2021.