Effect of GnRH analogs in advanced male breast cancer: 10-year experience from the Henan Breast Cancer Center and literature review

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To the Editor: Male breast cancer is relatively rare, accounting for just 1% of all breast cancer cases.[1] The management strategies for male breast cancer are mainly based on a limited number of retrospective studies and speculation based on female breast cancer. This study presents a comprehensive account of a decade-long observation of male metastatic breast cancer (mMBC) in our institution. The Affiliated Cancer Hospital of Zhengzhou University database had records of 2853 advanced breast cancer cases that were treated from January 1, 2010 to December 31, 2019. Out of the total number, 18 cases were identified as mMBC. The analysis encompassed data about the treatment administered, the treatment's effectiveness, and the patient's survival outcomes. The present investigation entails a retrospective examination of our institution's 10-year experience with patients diagnosed with mMBC and a comprehensive evaluation of relevant literature.

Of them, 15 cases included treatment-related information, including post-metastatic treatment. The American Joint Committee on Cancer (AJCC) breast cancer staging system was used for clinical staging, following the St.Gallen consensus criteria for molecular classification. The research study involving human participants underwent a thorough evaluation and received approval from the Medical Ethics Committee of Henan Cancer Hospital (No. 2017407). The informed consent was obtained from every patient.

Out of the initially recruited group of 18 patients, three were eliminated from the study due to insufficient data regarding treatment effectiveness or inability to continue participating. A total of 15 patients were subjected to the first endocrine therapy, which involved the administration of goserelin in conjunction with an aromatase inhibitor (AI) regimen. Three patients were still receiving first-line endocrine therapy at the close of the study. One patient received simultaneous cyclin-dependent kinase (CDK) 4/6 inhibitor (palbociclib) treatment. Five and four patients, respectively, underwent second-line and third-line treatment with endocrine therapy or chemotherapy. Two patients received fourth-line therapy.

All patients were followed up either at the hospital or by telephone. The follow-up time was between the initial consultation and the last follow-up or death. The follow-up end date was December 31, 2021. Disease-free survival (DFS) was the interval from diagnosis to first recurrence or metastasis. The progression free survival (PFS) was defined as the interval from the onset of therapy to disease progression or the date of the last follow-up. In contrast, the overall survival (OS) was defined as the interval between initial recurrence/metastasis and all-cause death or the date of the last follow-up. The objective response rate (ORR) was defined as the proportion of patients with confirmed complete or partial response according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), and the clinical benefit rate (CBR) was defined as the proportion of patients with confirmed complete response, partial response, or stable disease (≥6 months) according to RECIST 1.1. All statistical analyses were performed using IBM SPSS 22.0 (SPSS Inc., IBM Corp., Armonk, NY). The Kaplan–Meier method was utilized to conduct survival analyses.

The age of disease onset for the 18 patients ranged from 34 years to 70 years, with a median age of onset of 56 years. Of the enrolled patients, 14/18 were ≥50 years old. According to the St. Gallen consensus molecular categorization method for breast cancer, 17/18 of the patients in this research were positive for hormone receptors and negative for human epidermal growth factor receptor 2 (HR+/HER2–). In comparison, 1/18 were positive for HER-2.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000003005

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Chinese Medical Journal 2024;137(13)

Received: 24-09-2023; **Online:** 06-03-2024 **Edited by:** Ting Gao and Xiuyuan Hao

The study comprised a total of 15 patients who were eligible for evaluation. Out of them, 13 patients received initial treatment with goserelin and AIs, and among them, two patients experienced partial regression (PR), nine patients acquired stable disease (SD) during six months, and two individuals exhibited progressive disease (PD). The ORR was 2/13, indicating the proportion of patients who responded positively to the treatment. The CBR was 11/13, representing the percentage of patients who had a clinical benefit from the treatment. Furthermore, the median PFS (mPFS) was 22 months. After the first chemotherapy, the two remaining patients were administered a combined treatment of goserelin and AI.

Nine patients underwent second-line treatment with endocrine therapy or chemotherapy, while four underwent third-line treatment with endocrine therapy or chemotherapy. Of the four patients who received goserelin in combination with fulvestrant, the PFS values were 6 months, 8 months, 9 months, and 12 months, respectively. The median follow-up time was 48.5 months. The median overall survival time (mOS) of the 15 patients was 36 months. Cases 7 and 11 received the above fourth-line therapy. Of these 15 patients, 12 died, while three (Cases 1, 4, and 9) were still receiving first-line endocrine therapy at the close of the study, with survival time without progression exceeding four years [Supplementary Table 1, http://links.lww.com/CM9/B886].

A total of 18 patients with mMBC were diagnosed and treated at our center over 10 years. This accounted for a mere 0.63% of the overall breast cancer cases observed during the same period.[2] These findings align with previously published incidence rates.[3] It was found that the age of MBC onset ranged between 34 years and 70 years, with a median of 56 years, while the age of recurrence ranged from 42 years to 72 years (median: 59.5 years). Owing to a lack of routine screening and clinical awareness, the diagnosis of breast cancer is frequently delayed in males compared with females, leading to a greater likelihood of male patients being diagnosed with advanced disease. A prior study reported that the median age of onset for the condition was 55 years in China and 68 years in the rest of the world. The age of mMBC onset observed in our study was thus consistent with previous reports from China.

In this study, most patients were HR+/HER2–, while one showed HER-2 amplification. Previous studies have reported that estrogen receptor (ER) or progesterone receptor (PR) positivity is higher in male breast cancer than in female breast cancer, with the former being particularly common. The prevalence of HER-2 positive in males has been shown to range from 6.5% to 23.5%, which is comparatively lower than the observed rates in female breast cancer. The observed positivities of ER, PR, and HER-2 in our study were consistent with those previously described.

As male breast cancer is generally HR-positive, endocrine therapy should remain the first-line treatment choice for individuals with recurrent or metastatic disease unless patients have symptoms or visceral crises. Endocrine treatment for mMBC patients is similar to that used in women, using tamoxifen, AIs, and fulvestrant drugs. Male breast cancer generally shows higher estrogen levels than postmenopausal female breast cancer, which can be significantly lowered by AI administration. Third-generation AIs are currently the most frequently used. Of the patients in our study, 13 underwent first-line treatment with AIs in combination with gonadotropin-releasing hormone analog (GnRHa) treatment, resulting in an ORR of 2/13, CBR of 11/13, and mPFS of 22 months. According to the guidelines established by the National Comprehensive Cancer Network (NCCN), it is recommended that patients with mMBC get treatment that is comparable to that provided to postmenopausal women. This treatment approach involves combining AI and GnRH.

Notably, the present study observed chest wall recurrence in Case 1, who was 70 years old. Administration of an AI-GnRHa treatment led to a partial response in this case. However, after several months, the patient was unwilling to go to the hospital for injection, and when the GnRHa was stopped for two months, the check wall recurrence returned but decreased once more when GnRHa treatment was reinstated. The potential integration of AI in the management of mMBC may warrant exploring integrating AI with surgical or therapeutic orchiectomy as a viable approach.

In our study, the PFS after treatment with 500 mg of fulvestrant in combination with a GnRH analog in four cases was 6 months, 8 months, 9 months, and 12 months, respectively, with a median PFS of 8.5 months. The role of fulvestrant in mMBC treatment remains unclear. There are no data on the comparative effectiveness of fulvestrant alone or in combination with a GnRHa. A summary of the efficacy of fulvestrant in mMBC[4] showed that the dose of administered fulvestrant was equal to 250 mg monthly with a loading dose of 500 mg and the mPFS was five months. It is known that this dose is not optimal. Studies in large case series and the CONFIRM phase III trial suggested the potential usefulness of fulvestrant (a dose of 500 mg every 28 days plus an additional 500 mg on day 14 of the first month) for treating patients with mMBC.

The use of CDK4/6 inhibitors in combination with endocrine therapy has become the standard of care for individuals with advanced HR+/HER2– breast cancer. In the present study cohort, only one patient received this treatment with GnRHa as a second regimen. The treatment was well-tolerated, and the patient achieved PR with a PFS of 12 months. The 2020 American Society of Clinical Oncology for managing male breast cancer[5] recommends that cyclin-dependent kinase 4/6 inhibitors can be used in men similar to their use in women.

The study has several limitations. Specifically, it was a retrospective study conducted at a single institution. Furthermore, a lack of data about drug-induced adverse responses and molecular characteristics was also observed. However, the research discovered that the treatment protocols for metastatic male mMBC aligned with those employed for advanced female breast cancer. This

implies that these protocols could be a valuable resource for healthcare professionals managing mMBC.

In conclusion, mMBC in males is uncommon, with strategies for treatment adapted from advanced breast cancer in women and case series in men. The material from this case series has the potential to be beneficial as a reference for healthcare professionals treating mMBC. We will also continue monitoring mMBC patients' follow-up treatment and conducting genetic testing in our facility.

Acknowledgement

We would like to thank all the reviewers who participated in the review and MJEditor (www.mjeditor.com) for its linguistic assistance during the preparation of this manuscript.

Conflicts of interest

None.

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How to cite this article: Zhang MW, Lyu HM, Niu LM, Liu ZZ, Zeng HA, Zhao SN, Wang J, Sun HH, Yan M. Effect of GnRH analogs in advanced male breast cancer: 10-year experience from the Henan Breast Cancer Center and literature review. Chin Med J 2024;137:1623–1625. doi: 10.1097/CM9.0000000000003005