Journal of Contemporary Medical Practice (JCMP) ISSN: 2006-2745
DOI: 10.53469/jcmp.2024.06(12).46

Trastuzumab Deruxtecan (DS8201) Rescue Advanced Her2 Low Expression Breast Cancer: A Case Report and Review of Literature

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Abstract: ***HER2 low-expression subtype breast cancer has not yet been included in the guidelines, so there are fewer drugs available for this type of breast cancer. The new drug Trastuzumab deruxtecan (DS8201) can be used for the treatment of HER2 low-expression subtype breast cancer, which is suitable for patients with non-surgically resectable or metastatic HER2 low-expression subtype breast cancer. We hereby report a case of using Trastuzumab deruxtecan to rescue an advanced HER2 low expression subtype breast cancer patient in our clinical admission process, in order to provide new treatment ideas for HER2 low expression patients.***

Keywords: Trastuzumab deruxtecan, HER2 low- expressing breast cancer, Breast cancer brain metastasis, Breast cancer liver metastasis**.**

1. Introduction

Breast cancer is the most common malignant tumor in women and has the highest incidence in most countries [1]. About 15% of primary invasive breast cancers have human epidermal growth factor receptor 2(HER2) oncogene amplification or over expression [2], and these breast cancer patients can benefit from targeted therapy. However, there are some HER2-negative breast cancer patients with IHC "1+" level of HER2 and those with IHC "2+" level of HER2 but ISH-negative breast cancer (currently defined as HER2-overexpression) who cannot benefit from targeted therapy. benefit from targeted therapy. We believe that such a categorization has its shortcomings, and the new drug Trastuzumab deruxtecan has now been approved by the US FDA for the treatment of patients with non-surgically resectable or metastatic HER2 low- expressing subtypes of breast cancer[3].We now report a case of HER2-over expressing advanced breast cancer patient rescued by targeted therapy combined with traditional Chinese medicine during our clinical admission, in order to provide a new treatment idea for HER2-overexpressing patients.

2. Case Report

The patient was a 62-year-old woman, was admitted to the hospital on March 21, 2023, for "confusion for 1 week, more than 4 months after surgery for left breast cancer."

2.1 Medical History Review

The patient underwent a "left breast mass and left axillary lymph node fine needle aspiration biopsy" at our hospital on May 17, 2022. Routine pathology revealed cancer metastasis in the axillary lymphoid and fibrous tissue. The biopsy from the left breast mass and immunohistochemical results indicated invasive cancer cells expressing ER(-), PR(-), AR (approximately 1% positive), Ki67(approximately 40% positive), HER2 (2+), and FISH(-). Consequently, the patient received neoadjuvant chemotherapy in four cycles from May 18, 2022, to July 21, 2022, using the AC regimen, specifically: Cyclophosphamide (0.9g) and Liposomal Doxorubicin (55 mg). The efficacy evaluation of neoadjuvant chemotherapy was PR.From August 11, 2022,to September 8, 2022, the patient received three additional cycles of neoadjuvant chemotherapy using the Pregimen, specifically Liposomal Paclitaxel (240 mg). On September 19, 2022, the patient was admitted for the eighth cycle, and on September 20, a 1.5T breast MRI indicated multiple infiltrative cancer lesions in the left breast, which had increased in size compared to the August 10 images; multiple enlarged lymphnodes were also noted in the left axilla, some of which had increased in size (Figures 1 and 2). An ultrasound of the supra clav icu lar lymph nodes on September 24 revealed enlarged lymphnodes in the left supraclavicular fossa,with indeterminate nature. The fine needle aspiration cytology on September 24 indicated the presence of cancer cells,suggesting adenocarcinoma in light of the clinical history.After discussing the current condition and possible treatment options with the patient and their family, they chose to switch the chemotherapy regimen to Tcb, which included Paclitaxel (180mg on Day 1 and 8) and Carboplatin (500 mg on Day 1). The patient received two cycles of this new regimen on September 28 and October 19, 2022. The diagnosis of left breast cancer with axillary and supraclavicular lymph node metastasis was confirmed, and after nine cycles of neoadjuvant treatment, the efficacy assessment was SD. According to guidelines, surgical treatment was recommended. Therefore, on November 11, 2022, the patient underwent radical left mastectomy and radical left axillary lymph node dissection under general anesthesia. Postoperative pathology indicated: (1) Invasive breast cancer, not otherwise specified (invasive ductal carcinoma), Nottingham grading: grade 3 (3 points for gland formation, 3 points for nuclear grade, 2 points for mitotic count, total score 8), with treatment response (Miller-Payne grade 2: slight reduction in tumor cells, but overall cell count still high, with a reduction of less than 30%); tumor size 4. 5 cm × 3. 5 cm × 2 cm, with cancer thrombus in blood vessels and nerve infiltration by cancer. (2) No tumor involvement in nipple or skin; no residual tumor in surrounding or basal margins. (3) All 32 axillary lymph nodes showed cancer metastasis (32/32),

with treatment response (Sataloff grade: N-C grade). Immunohistochemistry results indicated invasive cancer expressing ER(-), PR(-), AR (approximately 5% positive), Ki67 (approximately 25% positive), HER2 (2+). Further chemotherapy was suggested, but the patient and family refused. Due to the COVID-19 pandemic, the patient was discharged. In January 2023, a hard mass was discovered in the left chest wall, with skin color changes and increased temperature; the nature of the mass was to be determined. Therefore, on January 18, 2023, the patient underwent excision of the left chest wall lesion, and intra operative rapid pathology indicated: (Left chest wall mass): presence of cancerous tissue, considering breast cancer invasion and/or metastasis based on history. The patient underwent 25 sessions of radiotherapy in the radiotherapy department.

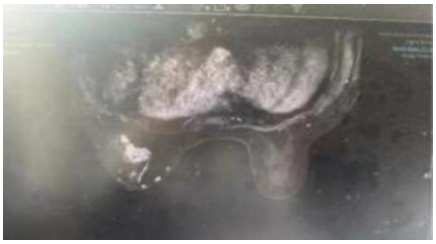

Figure 1: Breast MRI (2022-08-10)

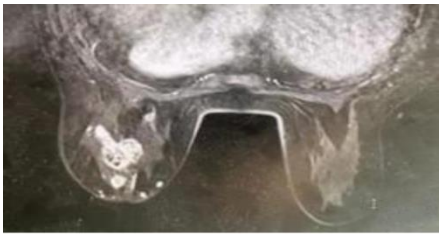

Figure 2: Breast MRI (2022-09-20)

2.2 Treatment Process

On March 14, 2023, the patient experienced dizziness, unclear consciousness, and unclear speech. After admission, a cranial MRI on March 22, 2023, indicated a small nodular lesion in the left parietal lobe, with a maximum size of approximately 23 mm×18 mm, surrounded by patchy long T1 and long T2 signal in the brain parenchyma. Mild displacement of the left lateral ventricle was observed, with no significant widening or displacement of the other ventricles, cisterns, or sulci (Figure 3). Considering the history, brain metastasis was suspected. An upper abdominal CT scan revealed a lesion in the right liver lobe, with a maximum diameter of about 2cm, also suspected to be a metastasis. According to existing guidelines, this patient is classified as having triple-negative breast cancer, but immunohistochemistry indicates low HER2 expression. Based on the DESTINY-Breast 04 trial, patients with low HER-2 expression receiving Trastuzumab deruxtecan treatment showed a higher mPFS compared to those receiving physician-selectedchemotherapy ($P<0.001$); the median OS in the Trastuzumab deruxtecan group was 23.4 months, compared to 16.8 months in the chemotherapy group ($P=0.001$) [4]. Currently, ASCO expert guidelines have recognized Trastuzumab deruxtecan[3]. We believe Trastuzumab deruxtecan is an effective drug for HER2 low-expressing patients. After fully consulting with the patient and family, the drug was purchased from Hong Kong, and on March 27, 2023, the patient received an intravenous infusion of Trastuzumab deruxtecan (300 mg). On April 17, 2023, the second targeted therapy was administered: Trastuzumab deruxtecan (300mg,intravenous infusion). Following treatment, an enhanced cranial MRI on April 20, 2023,indicated an abnormal enhancing lesion in the left parietal lobe, considering metastasis, which had slightly reduced compared to the previous MRI on March 22, 2023, with surrounding brain parenchyma edema (Figure 4). A CT scan of the upper abdomen showed slightly low-density masses and multiple nodular lesions in the liver, increased compared to the previous scan on March 22, 2023. On May 8, 2023, the patient received the third targeted therapy: Trastuzumab deruxtecan(300mg,intravenous infusion). On May 29, 2023, the fourth targeted therapy was administered: Trastuzumab deruxtecan (300 mg, intravenous infusion). On June 1, 2023, a cranial MRI showed the left parietal brain metastasis, with no significant progression compared to the previous scan (April 21, 2023). A full abdominal CT scan indicated multiple slightly low-density masses and nodular lesions in the liver, particularly in the right lobe, which had increased compared to the previous scan on April 21, 2023.

3. Discussion

3.1 Metastatic HER2 Low-Expressing Breast Cancer

Research shows that approximately one- third of patients with triple-negative metastatic breast cancer and about 15% of hormone receptor-positive, HER2- negative metastatic breast cancer patients experience brain metastases[5]. Over half of metastatic breast cancer patients have liver metastases, which typically occur in the later stages of the disease and have a poorer prognosis compared to soft tissue or bone metastases[6]. Metastatic breast cancer is unlikely to be cured, but systemic treatment can improve survival. In this case, we observed significant efficacy when Trastuzumab deruxtecan was initially used, with a substantial reduction in brain metastases (Figures 3),although its performance in treating liver metastases was mediocre. In later clinical treatments, we found that most breast cancer patients with liver metastases eligible for Trastuzumab deruxtecan did not benefit from targeted therapy.We believe the mechanism behind the control of brain metastases while liver metastases progressed requires further exploration.Additionally, the potential effects of Trastuzumab deruxtecan on metastases in other sites warrant further clinical observation.

3.2 Non-Metastatic HER2 Low-Expressing Breast Cancer

Multiple domestic studies indicate that HER2 low expression accounts for about 30% to 44% of all breast cancers [7-8]. Research by Zhu et al[9], found that HER2 low-expressing breast cancer constitutes nearly half of all breast cancers, with incidence rates significantly higher than HER2-positive breast cancer, exhibiting heterogeneity in clinical and pathological features. Among HER2 low- expressing breast cancers, there are also prognostic differences between hormone receptor-positive and triple-negative subtypes. Bai Bing et al [10] noted that hormone receptor-negative HER2 low-expressing patients have shorter DFS and OS. Similarly, differences exist between HER2 low-expressing and HER2 -negative breast cancers within the triple- negative category. Studies show that, excluding ER and PR-positive patients,

those with HER2 low expression have a significantly worse prognosis compared to those with HER2-negative expression [11-12]. Clearly, while this subtype is not included in current guidelines, treatment for HER2 low-expressing breast cancer should be emphasized. Ongoing research into the clinical and pathological characteristics of HER2 low-expressing patients is deepening, making further investigation into the efficacy of drugs like Trastuzumab deruxtecan in this population a promising direction for future exploration.

4. Conclusion

Human Epidermal Growth Factor Receptor 2(HER2) has been identified as a target in breast cancer, leading to the development of HER2-targeted therapies that have transformed treatment for HER2-positive breast cancer patients.There is increasing awareness of the prevalence of low HER2 expression in tumors, which may impact the benefits of HER2-targeted therapies.We anticipate that new and more potent drugs targeting HER2 low expression will emerge in the future. Furthermore, we believe it is crucial to refine the terminology surrounding HER 2 expression to optimize treatment for breast cancer patients based on their HER2 expression levels.

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