Pyrotinib in the Treatment of Refractory HER2-Positive Metastatic Breast Cancer: A Case Report

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Abstract

We present the patient with HR (-) / HER-2 positive breast cancer who received neoadjuvant chemotherapy, surgery, postoperative adjuvant trastuzumab and radiotherapy. Then she had multiple metastases and underwent multi-line rescue chemotherapy and anti-HER-2 therapy (trastuzumab, lapatinib, ado-trastuzumab emtansine). During the salvage therapy with pyrotinib, her peripheral blood ctDNA was detected. Tumor mutation load (TMB) decreased with the remission of the disease, and then increased again with the progression of the disease.

Keywords: HER2; Pyrotinib; Refractory breast cancer

Introduction

Overexpression of HER2 in breast cancer leads to more aggressive disease and a poorer prognosis [1]. The HER2-targeted, including trastuzumab, pertuzumab, lapatinib, and T-DM1, have significantly improved outcomes in patients with HER2-positive metastatic breast cancer. We report a case with HER2-positive breast cancer, who had acquired resistance to trastuzumab, lapatinib, T-DM1; benefiting from pyrotinib.

Case Report

A 45-year-old female patient underwent ultrasound-guided puncture of left breast mass (MRI 9 × 6cm), left axilla and left subclavian enlarged lymph node on September 10, 2014. The pathological diagnosis was left breast invasive ductal carcinoma, left axillary lymph node metastasis. The immunohistochemistry showed estrogen receptor (ER) negative, progesterone receptor (PR) negative, human epidermal growth factor receptor 2 (HER2) strongly positive (3 +), and Ki-67 was about 60%.

From October 2014 to January 2015, she was treated with 4 cycles of ATH (pirarubicin, docetaxel, trastuzumab) and 3 cycles of sequential TH (docetaxel, trastuzumab) as neoadjuvant therapy. The clinical efficacy was evaluated according to RECIST criteria, and partial response (PR) was achieved through breast MRI examination. She underwent modified radical mastectomy for left breast cancer on March 26th, 2015. The histopathology showed that invasive ductal carcinoma with grade II, Miller-Payne grade 2. It was no clear vascular invasion, but axillary lymph node metastatic carcinoma was 1/27. The immunohistochemistry showed ER (-), PR (-), HER2 (3 +), and Ki-67 was about 40%. She received adjuvant radiotherapy for left chest wall field and left superior and inferior clavicle field on May 25, 2015, and trastuzumab adjuvant therapy for one year.

In June 2016, CT scan and superficial ultrasound demonstrated multiple left lung and left cervical lymph nodes metastases. She initially received lapatinib combined with vinorelbine rescue therapy for 10 cycles, with the optimal efficacy of PR and PFS for 8 months. She was treated with second-line rescue therapy with GP (gemcitabine, cisplatin) for 6 cycles, with the efficacy of PR; then gemcitabine maintenance therapy for 2 cycles and PFS was 7 months. In September 2017, she was treated with HX(trastuzumab 21 days as a cycle, capecitabine 3500mg per day for 14 days, and rest for 7 days as a cycle) for 4 cycles, with the best effect of SD and PFS for 4 months. From January 2018, T-DM1 (21 days as a cycle of 260mg d1) rescue therapy was performed for 2 cycles, and the PFS was 1.5 months. From March 2018, the...
patient was administered with 500mg of oral apatinib once daily until the disease progressed again in May 2018. Subsequently, she underwent oral etoposide (75mg per day for 14 days, and rest for 7 days as a cycle) as sixth-line rescue therapy, simultaneously her left parietal brain metastases were treated with cyberknife. In July 2018, lung CT scan showed that the lung lesions significantly enlarged and the disease progressed. From August 2018, the patient was administered 400mg oral pyrotinib, once daily. One month later, lung CT demonstrated that the lung lesions had markedly shrunken in size, as shown in figure 1. The patient was treated with pyrotinib for 7 months and the disease progressed again. The patient’s peripheral blood ctDNA was detected during the treatment. Her condition was significantly relieved after one month of pyrotinib and the TMB was significantly declined compared with that before treatment (30.0Muts/Mb versus 1.0Muts/Mb). Seven months later, the disease progressed again, and the TMB was significantly increased again, reaching 31.0Muts/Mb (Figure 2).

Discussion

Fifteen percent to 20% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2) [2]. HER2-positive breast cancer shows an aggressive clinical behavior and has higher rates of recurrence and metastasis. Since the advent of trastuzumab, the prognosis of patients with HER2-positive breast cancer has been significantly improved. However, NCCN guidelines recommend T-DM1 treatment after resistance to trastuzumab, and trastuzumab or lapatinib can be used on the third and posterior lines. In China, T-DM1 has not been approved for listing, and the HER2-targeted therapies are only trastuzumab and lapatinib, which are far from meeting the treatment needs of patients with HER2-positive breast cancer.

Pyrotinib is a new drug independently developed in China, and it directly acts on the tyrosine kinase domain of the HER2 pathway and completely blocks downstream pathways activated by homodimers or heterodimers of EGFR, HER2, and HER4 on the tumor cell membrane [3,4]. The phase I study of pyrotinib [5] established the maximum tolerated dose as 400mg in patients with HER2-positive metastatic breast cancer and the overall response rate was 50.0%. The randomized, phase II study [6] showed that the objective responses and progression-free survival were increased in pyrotinib combined with capecitabine group than lapatinib group. Diarrhea was the most common adverse effect, mainly in grade 1 and grade 2. The molecular subtype of this patient was HR (-)/HER2 positive, and the disease-free survival (DFS) was 14 months. From June 2016, the patient had multiple metastases and underwent multi-line rescue chemotherapy and multiple anti-HER2 therapy (trastuzumab, lapatinib, T-DM1), which each drug was given until progressive disease (mainly enlarged pulmonary lesion). From August 2018, the patient was treated with 400mg of oral pyrotinib, once daily and she developed grade 1 adverse effects of diarrhea. One month later, lung CT demonstrated that the lung lesions had markedly shrunken in size. After 7 months of pyrotinib, the disease progressed again.

TMB refers to the number of somatic mutations in the coding area. Junnan Xu et al’s study [7] revealed that patients with high TMB had poor DFS (83 vs 59m, P=0.005), and the level of TMB was an independent risk factor for DFS. The patient with HER2 positive advanced breast cancer was treated with multi-line chemotherapy and multiple anti-HER2 therapy. The patient’s peripheral blood ctDNA was detected during the salvage therapy with pyrotinib. Her condition was significantly relieved after one month of pyrotinib, and the TMB was significantly declined compared with that before treatment (30.0Muts/Mb versus 1.0Muts/Mb). Seven months later, the disease progressed again, and the TMB was significantly increased again, reaching 31.0Muts/Mb. It is suggested that ctDNA TMB detection may be able to predict the efficacy of anti-HER2 treatment earlier than imaging examination. Based on the results of this case, a large sample size clinical study can be carried out to observe the predictive and prognostic role of fluid biopsy in anti-HER2 therapy.
Figure 1: A) CT (2018-7-27) demonstrates the largest lung metastasis before oral pyrotinib. B) Lung metastasis is significantly reduced in size after one month of pyrotinib. C) After 7 months of pyrotinib, CT (2019-3-12) scan reveals that lung metastasis is enlarged again.

Figure 2: Changes in TMB (Muts/Mb) before pyrotinib, one month and 7 months after pyrotinib.

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