Complete response in patient with liver metastasis of HER2-positive breast cancer following therapy with margetuximab: a case report

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Metastatic human epidermal growth factor receptor 2 (HER2) positive breast cancer has a poor prognosis and few effective targeted therapies. However, several anti-HER2 agents are emerging in conjunction with chemotherapy, which may lead to increased rates of pathological complete response in patients with HER2-positive metastatic breast cancer. Among them, margetuximab demonstrated a significant improvement in progression-free survival compared with trastuzumab, when combined with chemotherapy in pretreated patients. Here we present a case of a 67-year-old female patient who was diagnosed with HER2-positive, histological grade III and invasive ductal carcinoma of the left breast in September 2018. She received postoperative adjuvant therapy with EC-TH plus radiotherapy, followed by therapy with HER2-targeted trastuzumab for 1 year (till December 2019). In May 2020, routine reexamination showed a supraclavicular lymph node and bone metastasis. Patient was then treated with pyrotinib, capecitabine and bisphosphonate for a period of 3 months. In December 2020, liver MRI revealed multiple liver metastases. The patient received eight cycles of second-line therapy (vinorelbine plus margetuximab) from January 2021. Since the ninth cycle, the patient was continued with only margetuximab. In March 2021, MRI showed a 70% decrease in the liver metastasis lesions. By June 2021, liver lesions were totally disappeared. During therapy, patient experienced only grade-1 anemia. This case demonstrates that margetuximab plus chemotherapy is safe and might bring clinical benefits for patients with HER2-positive breast cancer with liver metastasis. Further studies evaluating the efficacy and safety of margetuximab in Chinese HER2-positive breast cancer patients are needed. *Anti-Cancer Drugs* 34: 883–887

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Introduction

Breast cancer is the most common cancer worldwide and fifth most leading cause of cancer-related deaths in China [1]. About 25% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2) due to ERBB2 gene amplification, which results in a more aggressive breast cancer phenotype [2]. The current standard first-line therapy for patients with HER2-positive metastatic breast cancer is a taxane, trastuzumab and pertuzumab anti-HER2 regimen combined with chemotherapy [3]. However, even after multiple lines of anti-HER2 therapy, HER2-positive metastatic breast cancer remains incurable [4].

Multiple novel anti-HER2 compounds have recently emerged for the treatment of patients with metastatic HER2-positive breast cancer [5]. Margetuximab, a novel, anti-ERBB2 monoclonal antibody, in combination with chemotherapy was recently approved by FDA for the treatment of patients with metastatic HER2-positive breast cancer who had received two or more anti-HER2 regimens [6]. Margetuximab plus chemotherapy demonstrated a significant improvement in progression-free survival (PFS) compared with trastuzumab plus chemotherapy in patients with metastatic HER2-positive breast cancer after progression on two or more prior anti-HER2 therapies [7]. The 2021 National Comprehensive Cancer Network (NCCN) V.2 breast cancer guidelines recommend margetuximab combined with chemotherapy as a third-line treatment regimen for HER2-positive metastatic breast cancer [8]. The 2022 Chinese Society of Clinical Oncology (CSCO) guidelines for the diagnosis and treatment of breast cancer recommend margetuximab

as the treatment option for HER2-positive, metastatic breast cancer after treatment failure [9]. Here, we present a case of patient with advanced HER2-positive metastatic breast cancer who progressed on trastuzumab and pyrotinib, and was treated with margetuximab combined with vinorelbine. The partial response (PR) was achieved after two courses of treatment, and the liver metastases disappeared after half a year, and the complete response (CR) status is still maintained, and margetuximab therapy is continued.

Case presentation

A 67-year-old postmenopausal female, with no family history of hereditary breast cancer was diagnosed with 'left breast nodule' in September 2018 and underwent modified left breast mastectomy plus axillary lymph node dissection. Postoperative pathology showed histological grade III of invasive ductal carcinoma of the left breast. High-grade ductal carcinoma *in situ* accounted for 5%. No definite intravascular tumor thrombus and no definite nerve invasion were detected on the biopsy section. The left breast nipple section submitted for examination showed no cancer involvement, and the ipsilateral lymph nodes were found to have metastatic cancer (35/48). Immunohistochemical staining demonstrated that cancer cells were estrogen and progesterone receptor-negative, HER2(3+) and Ki-67(80%). CD16A gene polymorphism test results of the patient demonstrated a CD16A-158F/F variant.

Given the HER2-positive status, the patient was initially scheduled to receive postoperative adjuvant therapy with epirubicin cyclophosphamide-taxol herceptin (EC-TH) plus radiotherapy (left chest wall + locking + internal breast D T50G y/25F), followed by therapy with HER2-targeted monoclonal antibody trastuzumab for 1 year (Fig. 1). The treatment was completed in December 2019. In May 2020, routine reexamination with computed tomography scan showed a supraclavicular lymph node and bone metastasis. The patient had a disease-free survival of 20 months.

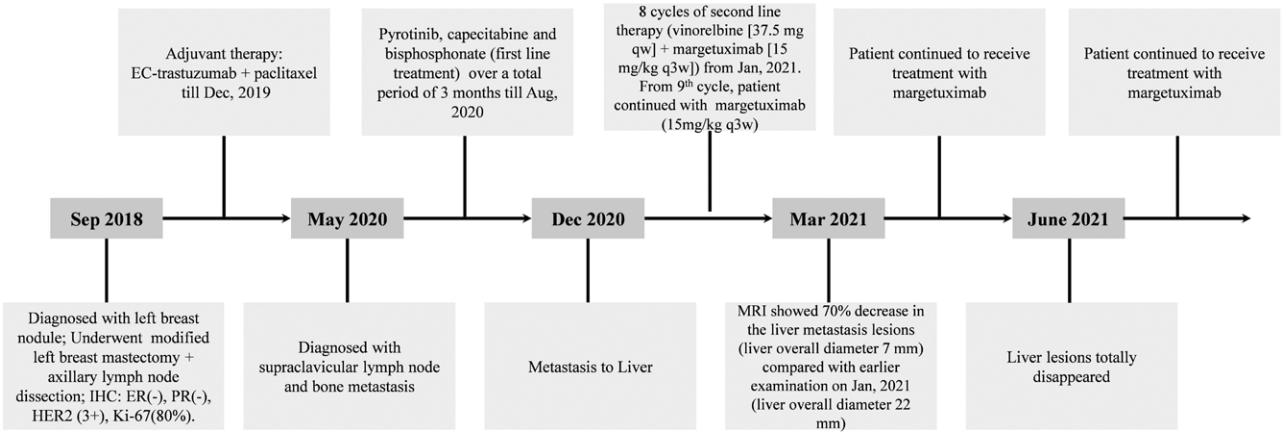
In May 2020, the patient was treated with pyrotinib (400 mg qd, Q3W), capecitabine (1000 mg/m^2 oral, bid, D1–14, Q3W) and bisphosphonate (first-line treatment) over a total period of 3 months. In December 2020, liver MRI of the patients revealed multiple liver metastases (Fig. 2). The patient discontinued the drugs due to diarrhea and had a PFS of 7 months.

In December 2020, the patient received eight cycles of second-line therapy (vinorelbine [37.5 mg qw] + margetuximab [15 mg/kg q3w]) from January 2021. Since the ninth cycle, the patient was reluctant to receive chemotherapy due to advanced aging and was continued with a single drug margetuximab (15 mg/kg q3w). During therapy, no serious side effects and only grade-1 anemia were observed. The PR was observed after two courses of treatment, and CR was observed after eight courses of treatment. In March 2021, MRI showed a 70% decrease in the liver metastasis lesions (liver overall diameter 7 mm) compared with previous examination on 5 January 2021 (liver overall diameter 22 mm). By June 2021, liver lesions totally disappeared. To date, the patient continued to receive treatment with margetuximab.

Discussion

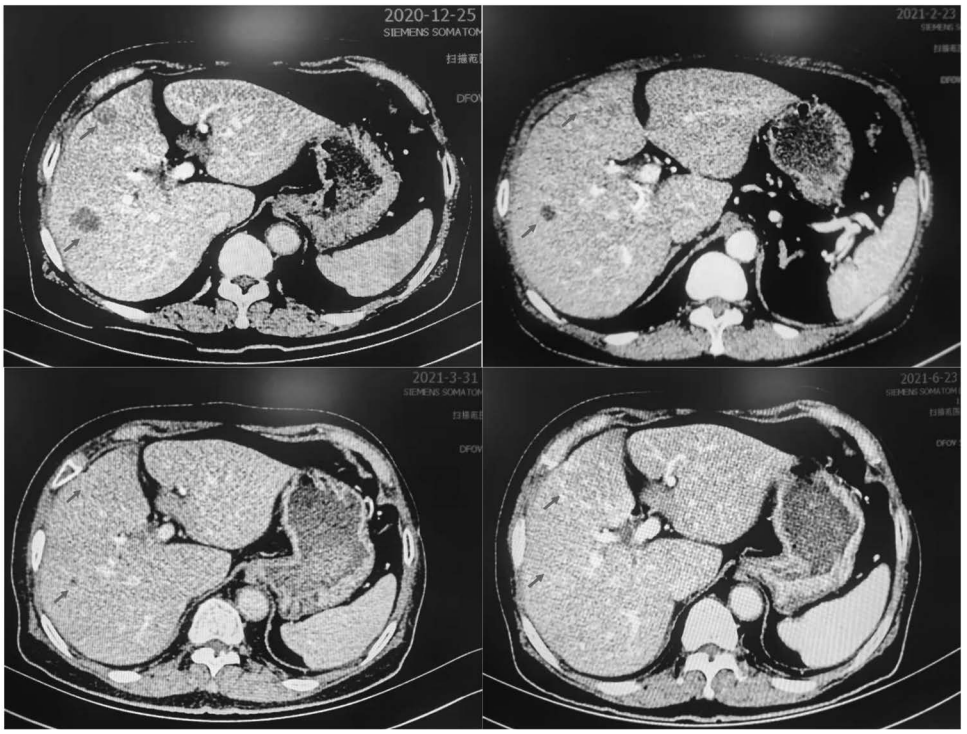
Around 20% of breast cancer patients will experience relapse, and 50–70% of metastatic breast cancer cases involve the liver metastasis [10]. Historically, patients with HER2-positive breast cancer have poor prognosis following metastasis to the liver, with a median survival rate of 2–3 years [11]. Tumor response and patient survival have significantly improved with the advent of HER2-targeted therapies [7,12,13].

Fig. 1



Patient course of disease progression and various treatment timelines received. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PR, progesterone receptor.

Fig. 2



Target lesion (liver) response evaluation during margetuximab treatment. 25 December 2020: liver overall diameter 22 mm; 23 February 2021: liver overall diameter reduced to 10 mm; 31 March 2021: liver overall diameter reduced to 7 mm; and 23 June 2021: liver lesions completely disappeared.

Margetuximab is a chimeric, Fc-engineered, immune-activating, anti-receptor tyrosine kinase erbB-2 protein (ERBB2) monoclonal antibody. Fc-engineering of margetuximab through substitution of 5 amino acids (L235V, F243L, R292P, Y300L and P396L) from wild-type IgG1 in the Fc domain enhances CD16A receptor affinity (especially CD16A-158F), and reduces affinity for CD32B receptor, thereby enhancing antibody-dependent cellular cytotoxicity effect and adaptive anti-ERBB2 immune responses [14,15]. Single nucleotide polymorphisms in the coding regions of Fc receptor genes have been associated with varied affinities that can impact the clinical response to several IgG1 monoclonal antibodies, such as trastuzumab and margetuximab [2]. Two CD16A polymorphisms at amino acid 158 encode two alleles, which include a higher-affinity valine (V) variant and a lower-affinity phenylalanine (F) variant. Correlation between efficacy and CD16A polymorphism in trastuzumab-treated advanced breast patients indicates lower immune activation in CD16A-158F allele carriers compared to those homozygous for the V158 genotype [2,16–18]. Poor clinical response to trastuzumab for these CD16A-158F carriers indicates these patients may benefit from an antibody with enhanced Fc-dependent immune activation [2].

A major benefit with Fc-engineered margetuximab is increased binding to all CD16A-158 V/F variants, compared with wild-type IgG1 [5]. Preclinical studies demonstrated that margetuximab was more effective compared with trastuzumab in the effector cells of both heterozygous or homozygous donors for the lower-affinity F variant [14]. Furthermore, compared with trastuzumab, margetuximab had stronger cytotoxic effects and enhanced HER2-specific B-cell and T-cell–mediated responses in all CD16A genotype expression groups, including trastuzumab-resistant and HER2 low-expressing cells [14,19].

A previous randomized, phase-3, trial (SOPHIA) compared the efficacy of margetuximab plus chemotherapy versus trastuzumab plus chemotherapy in patients with HER2–positive advanced breast cancer [7]. Margetuximab plus chemotherapy had a statistically significant improvement in PFS with a 24% relative risk reduction [5.8 vs. 4.9 months, with a hazard ratio (HR), 0.76; 95% confidence interval (CI), 0.59–0.98; $P = 0.033$] than trastuzumab plus chemotherapy. Significant higher response rates (25.2% vs. 13.7%; $P = 0.0006$) were reported with margetuximab. Notably, most people of the world's population (80–90%) carry the CD16A-158F allele, the study benefits were enhanced in patients with low-affinity CD16A-158F genotypes (median PFS 6.9 vs. 5.1 months, with HR, 0.68; 95% CI, 0.52–0.90; $P = 0.005$) [7]. In early phase-I trial and even in SOPHIA

trial, margetuximab demonstrated acceptable safety, as the most frequent toxicities were grade 1 and grade 2 including, especially, pyrexia, nausea, anemia, diarrhea and fatigue [7,20]. In the line light of these observations, during therapy, our patient had also experienced only grade-1 anemia, but not serious side effects.

The survival rate of HER2-positive breast cancer patients with liver metastasis has increased and better curative effects were reported due to medical advances and targeted therapies [21]. Similarly, in response to margetuximab therapy, our patient had a CR and liver metastatic lesions were completely disappeared.

CSCO, NCCN guidelines recommend margetuximab to be used by patients with HER-positive breast cancer as a third-line treatment. However, our patient is of a second-line group and had a good response to margetuximab therapy. Given the observation with our case, patients undergoing second-line treatment might be considered for margetuximab therapy for better clinical outcomes.

Since margetuximab has shown promising efficacy results, an ongoing phase II (NCT04262804) study is being carried out to evaluate the safety and efficacy of margetuximab in Chinese HER2-positive breast cancer patients.

Conclusion

The role of HER2-targeted agents such as margetuximab in combination with chemotherapy will increase the resectability of liver metastasis. The success of this case suggested that margetuximab might bring clinical benefits for patient with advanced HER2-positive metastatic breast cancer. Further studies evaluating the efficacy and safety of margetuximab in Chinese HER2-positive breast cancer patients are needed, particularly in those with metastatic HER2-positive breast cancer who had received two or more anti-HER2 regimens.

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Ethics approval: all procedures performed in studies involving human participants were in accordance with the ethical standards of the Union Hospital Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China.

Consent for publication: a written informed consent was obtained from patient.

Data availability: the datasets generated during and/or analyzed during the current will be made available from the corresponding author upon a reasonable request.

Conflicts of interest

There are no conflicts of interest.

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