Life-threatening metastasis was suppressed by trastuzumab containing regimen in a patient with Her2-negative breast cancer

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Abstract A 49-year-old female was referred to our hospital with left breast cancer and subsequently underwent mastectomy and axillary dissection. The pathological findings showed invasive breast cancer with lymph node metastasis (2/22), nuclear grade 3, ER (6+) PgR (2+) for the Allred score, and Her2 (2+) in an immunohistochemistry. We determined the subtype of Her2-negative breast cancer according to the fluorescent in situ hybridization results, as follows: Her2/CEP17 ratio $1.1 < 2.0$. The patient received the EC regimen followed by docetaxel, and toremifene was subsequently administered. One year after the operation, the CA15-3 level was elevated at 50 ng/ml, and CT revealed liver metastases. Disease progression was not suppressed by paclitaxel containing regimen and eribulin. Then, we subsequently sought to determine whether the metastatic lesion showed the Her2 expression. Although the Her2 expression in the axillary lymph node metastases showed heterogeneous staining, the results were judged as Her2 (1+) according to the ASCO/CAP guidelines. We decided to administer trastuzumab and docetaxel due to the patient's life-threatening status, after which the CA15-3 level decreased and the symptom of fatigue improved. A total of 9 cycles of trastuzumab and docetaxel were administered, followed by maintenance trastuzumab continued to the present time. Physicians should be aware of the statement in the ASCO/CAP guidelines that the clinical decision to ultimately consider

Her2-targeted therapy should be individualized according to the patient's status.

Keywords Her2-negative breast cancer · Trastuzumab · Discordance

Introduction

Target therapy for human epidermal growth factor 2 (Her2) in breast cancer has progressed since trastuzumab was approved in 2001 [1]. The survival benefits of trastuzumab were confirmed by several clinical trials [2–4]. Trastuzumab containing regimen had been a standard therapy on perioperative adjuvant setting as well as recurrent stage for the patients with Her2 positive breast cancer.

The indication of trastuzumab is determined based on the expression of Her2 which is judged according to the ASCO/CAP criteria [5]. However, some patients with primary breast cancer judged to be Her2-negative who may receive benefits from Her2-targeted therapies are missed [6]. These misdiagnosis may be due to accuracy of Her2 testing or discordance of Her2 expression of metastatic lesion. Therefore, the ASCO/CAP guidelines for assessing Her2 amplification were changed in 2013, and indicated the need for repeat biopsies of metastatic lesions [7]. Furthermore, the guideline recommends that clinical decision to ultimately consider Her2-targeted therapy be individualized according to the patient's status (comorbidities, prognosis, and so on) [7].

We herein report the case of a patient diagnosed with Her2-negative breast cancer with Her2 (2+) on immunohistochemistry (IHC) and negative results on fluorescent in situ hybridization (FISH), whose life-threatening metastases were suppressed with trastuzumab containing chemotherapy.

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Case report

49 females were referred to our hospital with the left breast cancer diagnosed by fine needle aspiration cytology (FNAC). Mammography showed a tumor shadow with segmental pleomorphic calcification in the upper lateral quadrant, judged to be category 5. Computed tomography (CT) demonstrated axillary metastasis, with no other metastases. The patient underwent mastectomy and axillary dissection. The pathological findings showed invasive breast cancer with lymph node metastasis (2/22), nuclear grade 3, ER (6+) PgR (2+) for the Allred score, and Her2 (2+) on the IHC (Fig. 1a, b). According to the FISH results as follows: Her2/CEP17 ratio $1.1 < 2.0$ (Fig. 1c), we diagnosed her with Her2-negative breast cancer, and administered the EC regimen (epirubicin 90 mg/m^2 , cyclophosphamide 600 mg/m^2) for four cycles followed by docetaxel

(75 mg/m^2) for four cycles. Toremifene was subsequently administered (Fig. 2).

One year after the operation, the CA15-3 level was elevated at 50 ng/ml , and CT revealed liver metastases (Figs. 2, 3a). We administered bevacizumab and paclitaxel for four cycles; however, the CA15-3 level continued to be elevated at 104 ng/ml . We, therefore, changed the regimen to eribulin as the second-line therapy; however, she developed wheezing as an allergic reaction to this drug (Fig. 2). CT indicated the progression of liver metastases (Fig. 3b).

We subsequently sought to find the Her2 expression of axillary lymph node metastasis at the operation. Although the Her2 expression in the axillary lymph node metastases showed heterogeneous staining $<10\%$ of tumor cells (Fig. 4a–c), it was judged to be Her2 (1+) according to the ASCO/CAP criteria. Additionally, the Her2 level was slightly elevated at 26 ng/ml .

Fig. 1 **a** Pathological findings of primary breast cancer indicating invasive ductal carcinoma with nuclear grade 3 (G3). **b** Immunohistochemistry (IHC) for Her2 on the specimen of the primary breast

cancer indicated Her2 (2+). **c** Fluorescent in situ hybridization (FISH) for Her2 on primary breast cancer; Her2/CEP17 ratio; $1.1 < 2.0$ indicating no over expression of Her2

Fig. 2 Clinical course with the change of serum CA15-3. ① EC regimen (epirubicin 90 mg/m², cyclophosphamide 600 mg/m²)/3 weeks for 4 cycles. ② Docetaxel (75 mg/m²)/3 weeks for 4 cycles. ③ Toremifene 40 mg po. ④ Bevacizumab (10 mg/kg) + paclitaxel (90 mg/m²) regimen/4 weeks for 4 cycles. ⑤ Eribulin (1.4 mg/m² day 1, 8) for 1 cycle. ⑥ Docetaxel (75 mg/m²)/3 weeks for 9 cycles. ⑦ Trastuzumab (8 mg/kg initial dose and 6 mg/kg maintenance dose)/3 weeks for 22 cycles

Fig. 3 **a** Contrast enhanced CT revealed multiple liver metastases. *Black arrays* indicated metastatic lesions before the treatment of bevacizumab and paclitaxel regimen. **b** Liver metastases were

enlarged after the bevacizumab and paclitaxel regimen and eribulin. **c** Liver metastases were distinguished on CT findings after the administration of trastuzumab and docetaxel for 9 cycles

Fig. 4 **a** IHC for Her2 in the specimen of the axillary lymph node metastases, indicated heterogeneous staining. **b** The small part of cancer cells showed circumferential staining. **c** However, most of the

cancer cells were stained weakly, judged to be Her2 (1+) according to the ASCO/CAP criteria

The CA15-3 level remained elevated and the patient's symptom of fatigue increased. We decided to administered trastuzumab and docetaxel due to the patient's life-threatening status, after which the CA15-3 level decreased and the

symptom of fatigue improved. The serum Her2 level also decreased to 15 ng/ml. A total of 9 cycles of trastuzumab and docetaxel were administered, followed by maintenance trastuzumab continued to the present time (Fig. 2).

Discussion

This case indicates the existence of tumor heterogeneity and discordance between the primary tumor and metastatic sites, and the criteria for the Her2 expression according to the ASCO/CAP do not cover all patients who may receive benefits from Her2-targeted therapies [8].

Discordance in the hormone receptor and Her2 expression between the primary tumor and metastatic sites has been reported in several papers [9–12]. The rate of discordance is estimated to be approximately 20–30 % for hormone receptors and 10 % for Her2 expression [13]. According to a review paper by Yao et al. [14], the rate of discordance of the primary tumor and synchronous axillary lymph node metastases is around 20 % for hormone receptors and 10 % for Her2 expression. And positive changes in the synchronous axillary LN are a predictive factor for a good prognosis, whereas negative changes predict a worse prognosis. The authors highlighted the importance of examining the HR and Her2 expression in the axillary LNs as well as the primary tumors.

Krishnamurthy et al. reported that a rate of Her2 discordance in circulating tumor cells (CTC) and disseminated tumor cells (DTC) was around 20 % [15]. Furthermore, there are cases suggesting the possibility that Her2-positive cells in the cancer tissue diagnosed Her2-negative breast cancer spread easily to form distant metastases.

The level of serum Her2, formed from the cleavage of the extra-cellular domain (ECD) of the Her2 receptor, is measured using an enzyme-linked immunosorbent assay (ELISA) [16]. Elevation of the serum Her2 level is noted in 30 % of primary breast cancers and 51 % of metastatic breast cancers, and serum Her2 elevation is seen in 30 % of patients with metastatic disease whose primary breast cancer is negative for the Her2 expression. It remains controversial whether elevation of the serum Her2 level indicates the Her2 expression corresponding to metastatic disease. Therefore, further clinical trials are needed to confirm the validity of serum Her2 as a biomarker for selecting Her2-targeted therapies.

The ASCO/CAP guidelines for assessing Her2 amplification were changed in 2013 [7], as several reports have suggested the existence of patients expected benefits from Her2-targeted therapies who were missed according to the past criteria [17].

Although the present patient was Her2 (2+) and FISH-negative, the Her2 expression was judged as negative based on the new guidelines. Due to the patient's life-threatening condition, we decided to start the treatment with trastuzumab containing regimen taking into consideration the heterogeneous expression of Her2 in the axillary LN and

elevated serum Her2 level. Consequently, the life-threatening metastases were suppressed and the patient exhibited prolonged survival.

The ASCO/CAP guidelines recommend that clinical decision to ultimately consider Her2-targeted therapy be individualized according to the patient's status (comorbidities, prognosis, and so on) [15].

The clinical course of the present patient is considered to support this statement.

Conflict of interest The authors declare no conflicts of interest (COI).

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