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Case Report

Pathological Complete Response of HER2 Positive Breast Cancer to Trastuzumab emtansine and Endocrine Therapy after Progression to Standard Neoadjuvant Chemotherapy and Dual Blockade of HER2

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Abstract

We report a case of pregnancy-associated breast cancer with no response to neoadjuvant chemotherapy. Breast cancer progression during standard neoadjuvant treatment is not a frequent event. A 37-year-old woman with bilateral invasive carcinoma of no special type (NST) of the breast was referred to our Oncology Department. The immunohistochemistry indicated positive staining for Estrogen Receptor (ER) and Progesterone Receptor (PR) as well as positive Human Epidermal Growth Factor Receptor 2 (HER2). The patient was diagnosed during her first trimester of pregnancy and she decided to suppress it. The tumor experimented significant growth, during the treatment nowadays considered as standard, followed by an impressive response with the administration of Trastuzumab emtansine (T-DM1) combined with endocrine therapy (tamoxifen and goserelin). Although in the usual clinical practice the joint administration of chemotherapy and hormonal treatment is not recommended, in our patient we thought that it could be a reasonable alternative due to chemoresistance shown by the tumor as well as its development during pregnancy.

ABBREVIATIONS

NST: No Special Type; ER: Estrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receptor 2; T-DM1: Trastuzumab emtansine; pCR: Complete Pathological Response; IBC: Inflammatory Breast Cancer; MRI: Magnetic Resonance Imaging; GnRH analogue: Gonadotropin Releasing Hormone Analogue; OS: Overall Survival; DFS: Disease Free Survival; EFS; Event Free Survival; HR: Hazard ratio; CI: Confidence Interval; PFS: Progression Free Survival; TCHP: Carboplatin, Docetaxel, Pertuzumab, Trastuzumab

INTRODUCTION

Breast cancer is the second most common malignancy after cervical cancer during pregnancy [1]. It has been related to worse prognosis especially by late diagnosis. However, the prognosis of pregnant women does not seem to differ from that of non-pregnant patients when matched for age and stage of the disease [2]. Treatment of patients with breast cancer during pregnancy should be personalized. Today neoadjuvant treatment is considered standard and the number of patients who are receiving it is increasing. Currently the administration of chemotherapy and dual blockade of HER2 is recommended in tumors with HER2 overexpression, followed by surgery, then trastuzumab for 1 year and endocrine therapy if ER and/or PR are positive. In the same way, patients who are candidates for radiotherapy will receive it. Breast cancer progression during standard neoadjuvant treatment is not a usual event. In a published study with 1982 patients, only 3% of patients progressed while receiving at least one regimen [3]. Sometimes we have to face this situation, for

which there are no specific recommendations. In this report we present a case of pregnancy-associated triple positive breast cancer (HER2, ER and PR positive) with disease progression during neoadjuvant treatment based on dual blockage of HER2, doxorubicin and taxane, and later pathological complete response (pCR) with an alternative regimen based on endocrine therapy and T-DM1.

CASE PRESENTATION

A 37-year-old pregnant woman with no significant medical history diagnosed of breast cancer was referred to our institution. The patient noticed a rapid increase in the size of her left breast and consulted her gynecologist. During exploration, it was discovered that an erythema occupied at least one third of the left breast as well as edema with an underlying palpable mass and we performed an ultrasound. It showed a mass in each breast and we realized a bilateral biopsy. A high grade inflammatory breast carcinoma (IBC) was diagnosed in the left breast. The hormone receptor assay indicated that the tumor was positive for both ER (80%) and PR (30%), and also positive results were obtained on HER2 testing by immunohistochemistry (Figure 1). The Ki-67 expression index was 70%. The study of axillary lymph nodes was positive in the left side. In the contralateral breast we observed a NST carcinoma of 3 cm without suspicious axillary nodes. The immunohistochemical staining was consistent with positive ER (70%), RP (10%) and overexpression of HER2.The bone scintigraphy and Computer Tomography body were negative for metastases. The patient's levels of tumor markers were within the normal ranges. Even though the patient had previously received different treatments for sterility, she decided to terminate the pregnancy, because of the tumor. Although she had no family history of cancers, nevertheless as a 37-year-old patient with bilateral breast cancer she was referred to our Genetic Counseling Unit where she was assessed and after testing *BRCA1* and *BRCA2* genes, no pathogenic variants were detected. We completed the study with Magnetic Resonance Imaging (MRI) and Fine Needle Aspiration of the lymph node in the left axillar region. The definitive diagnosis was: left NST IBC with axillary affectation (cT4dN1M0-IIIB) and right NST breast carcinoma cT2N0M0-IIA, both of them triple positive (ER, PR and HER2 positive). In November 2015 we prescribed the first cycle of chemotherapy with doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks, and after the third cycle we confirmed clinical progression with tumor growth in the left breast. We decided to prescribe docetaxel 75mg/m^2 with trastuzumab 8 mg/Kg loading dose, followed by 6 mg/Kg, and pertuzumab 840 mg loading dose, followed by 420 mg every three weeks. During this treatment the patient developed new bilateral lesions in her thoracic skin, of which we took a biopsy obtaining the same histology and immunohistochemistry results as the initial tumor, without disease in other areas of the body. We sent the biopsies to another center, and they confirmed the results, in addition fluorescence in situ hybridization (FISH) was realized and the result was HER2 amplified. Because of chemoresistance and development of the tumor during the pregnancy we undertook a second line of treatment based on T-DM1 plus tamoxifen and Gonadotropin releasing hormone analogue (GnRH analogue). The clinical and radiological response was complete following 6 cycles of treatment including the disappearance of the skin nodes (Figure 2).

We discussed the case with the gynecologist and in spite of atypical evolution and skin nodes we believed that surgery could be considered. A bilateral mastectomy, left axillary lymphadenectomy and sentinel lymph node dissection in the right axillary region, was performed on 9 September 2016. Histopathological examination indicated that there was no residual tumor in breast neither in axillary nodes. Therefore, the residual burden cancer was 0. The patient received radiation therapy to the bilateral chest wall and regional nodes on the left. One year later, the plastic surgeons of our institution performed bilateral breast reconstruction with a latissimus dorsi musculocutaneous flap and implanted prostheses. To date the patient has not relapsed and continues treatment based on tamoxifen plus GnRH analogue and subcutaneous trastuzumab.

DISCUSSION

Breast cancer is the most common non-cutaneous malignancy among women, but fortunately most of the cases are diagnosed in early stages with a 5-year survival-rate of almost 90% [4]. Breast cancer is the second most common malignancy affecting pregnancy [1]. Pregnancy-associated breast cancer is defined as breast cancer that occurs during pregnancy or one year after delivery. The prognosis of pregnant women does not seem to differ from that of non-pregnant patients when matched for age and stage of the disease [2]. In patients requiring chemotherapy initiation during the first trimester, pregnancy termination would be considered. The planning of the ideal treatment requires a multidisciplinary team which includes an obstetrician and neonatologist in addition to oncology team [5]. The final decision should be made by the patient, after having been adequately informed. In our case, the patient decided to end the pregnancy, especially since it was the first trimester and she was suffering from IBC which is linked to a poor prognosis.

In clinical practice, a clear increase in the use of neoadjuvant chemotherapy is taking place. We know that the overall survival (OS) and disease-free survival (DFS) is the same for both adjuvant and neoadjuvant chemotherapy, with an insignificant increase in local recurrence for the second one [6]. The advantages of this choice of treatment are multiple; in vivo assessment of breast tumor response, early control of micro metastatic disease and improved surgical outcomes with a greater number of conservative surgeries for patients who were not previously eligible. In addition, the general consensus is that patients with IBC without evidence of distant metastases at the time of diagnosis should receive systemic chemotherapy followed by surgery and radiation therapy [7]. Due to them, we decided initiate neoadjuvant treatment. It is very uncommon to observe progression during the neoadjuvant treatment. In a study conducted in M. D. Anderson Cancer Center, only 3% of breast tumors progressed while they were administering the systemic treatment, and 55% of them responded to a second line of treatment [3]. Therefore, this event should allow us to change the regimen and obtain a pCR. Clearly, reaching a pCR improves the prognosis compared to patients who have residual disease, with better DFS in the HER2 positive and triple negative (ER, PR and HER2 negative) subgroups [8]. For this reason, the main objective of neoadjuvant trials is to achieve pCR.

Among patients with locally advanced tumors with

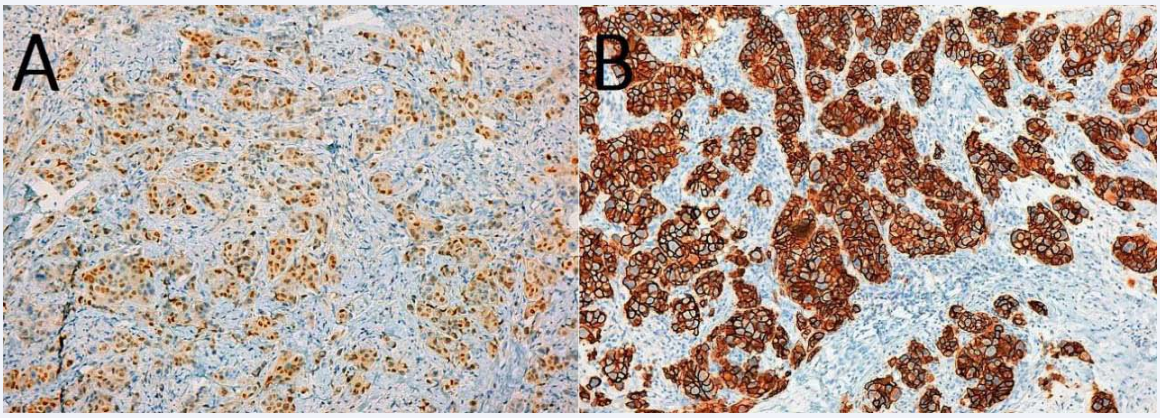

Figure 1 Immunohistochemistry tumor cells obtained from the biopsy of the mass of the left breast (H&E magnification, x 100) were ER positive (A), with overexpression of HER2 (B).

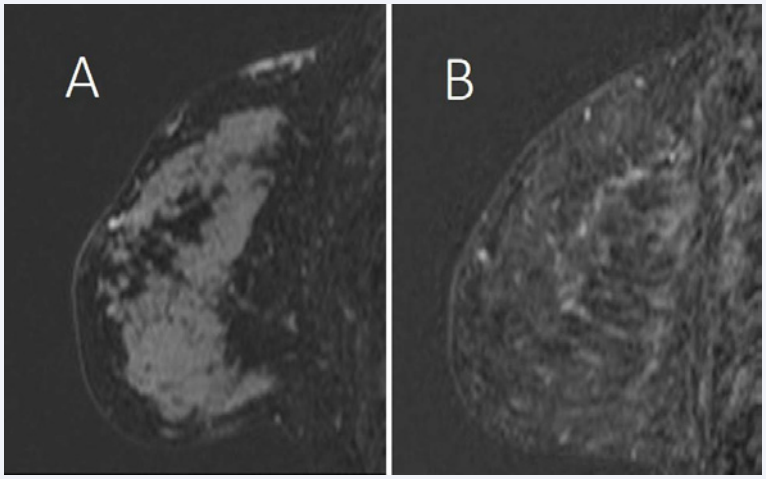

Figure 2 (A) – MRI of the left breast: a diffuse mass and skin nodes after docetaxel, pertuzumab and trastuzumab treatment. (B) - MRI after 6 cycles of treatment based on T-DM1 and endocrine therapy with complete response including the disappearance of the skin nodes.

overexpression of HER2, the role of treatment with trastuzumab was established after the NOAH trial. The results of the study showed an increase in pCR (39 vs 20%) and a benefit in event-free survival (EFS) from trastuzumab-containing neoadjuvant therapy followed by adjuvant trastuzumab in patients with locally advanced or IBC. Five-year EFS was 58% in the trastuzumab containing group versus 43% in the group of chemotherapy without trastuzumab, (Hazard Ratio (HR): 0.64, 95% Confidence Interval (CI) 0.44 to 0.93), and provided new insight into the association between pCR and long-term outcomes in HER2-positive disease [9].Increased effectiveness in pCR rates of dual anti-HER2 agents over single blockade has been recently reported in clinical studies, even if the tolerance is worse [10, 11]. We need to identify the patients who will benefit from it and thus be able to avoid toxicity to those who will not.

In metastatic HER2-positive breast cancer phase III CLEOPATRA trial showed an OS benefit of 56.5 months in the trastuzumab/pertuzumab arm compared with 40.8 months in the trastuzumab cohort (HR: 0.68; 95% CI, 0.56 to 0.84; p<0.001), and the same for progression free survival (PFS) 18.5 months vs 12.4 (HR: 0.68; 95% CI 0.58 to 0.80; p<0.001) [12]. The next step was to research the role of this drug in the neoadjuvant setting. In the NeoSphere trial, patients given pertuzumab and trastuzumab plus docetaxel had a significantly improved pCR (45.8%) compared with those given trastuzumab plus docetaxel (29%) (p=0.0141) [13]. The TRYPHAENA trial confirmed the cardiac safety of pertuzumab administration in regimens containing anthracyclines [14]. Due to these two [12-14] and subsequent studies, pertuzumab in combination with trastuzumab and taxane is currently approved in the metastatic and neoadjuvant treatment of HER2-positive breast cancer. In NeoSphere trial non-responders (including unknown) was 12% [13]. Nevertheless, the result in our patient was not as expected, the tumor progressed during the initial treatment. Nowadays the recommended treatment in second line is T-DM1, because of the phase III EMILIA trial´s results, with improved OS (30.9 vs 25.1 months (HR: 0.65; 95% CI 0.55 to 0.77; p<0.001) and PFS 9.6 vs 6.4 months (HR: 0.68; 95% CI 0.55 to 0.85; p<0.001), with better tolerability than the treatment at that time considered standard: capecitabine plus lapatinib [15]. However, in this trial patients previously treated with pertuzumab were not included. On the

other hand, there is evidence about the activity of T-DM1 after treatment based on pertuzumab, with a tumor response rate of 17.9% in overall population and 23.1% if we analyze T-DM1 as second line [16].

In our patient with triple positive breast cancer, we confirmed resistance to anthracycline, taxane and dual blockade of HER2. It has been found that ER+/HER2+ tumors are less likely to respond to dual HER2 blockade than ER-/HER2+ tumors because ER may act as a pathway of resistance to anti-HER2 treatment and the magnitude of benefit of dual blockade of HER2 will be smaller in these tumors [17]. The pCR rate in tumors with hormonal receptor positive is significantly lower compared to other subtypes. There are some trials in this setting without chemotherapy. In the TBCRC006 trial, women with stages II to III HER2-positive breast cancers received trastuzumab and lapatinib for 12 weeks. Women with ER-positive tumors also received letrozole (plus a luteinizing hormone-releasing hormone agonist if premenopausal). However, pCR rate was low in the subgroup of tumors with ER- (21%) [18]. In the Phase II PAMELA trial, patients were given lapatinib and trastuzumab for 18 weeks; hormone receptor-positive patients were additionally given letrozole or tamoxifen if premenopausal. The results suggest that HER2-enriched subtype, determined with the PAM50 subtype predictor can identify patients with HER2-positive breast cancer who are likely to benefit from dual HER2 blockade therapies, without need of chemotherapy [19].

In our case after disease progression we asked for new biopsy and repeat immunohistochemistry and tested HER2 amplification by FISH. We confirmed that the NST carcinoma was triple positive and due to the appearance of the tumor during pregnancy (extensive relationship with hormone levels) and proved chemoresistance, we decided to consider endocrine treatment without forgetting the anti-HER2 blockade.

In the literature, in the field of breast cancer neoadjuvant treatment there are two main studies that are characterized by combining anti-HER2 blockade, chemotherapy and endocrine treatment. In the Phase III NSABP B-52, the patients were randomized to carboplatin, docetaxel, pertuzumab, trastuzumab (TCHP) and estrogen deprivation therapy determined by menopausal status versus the same regimen without endocrine treatment. The primary endpoint was pCR in resected breast and nodes. In this study the addition of estrogen deprivation to neoadjuvant treatment did not increase toxicity, and was not antagonistic, but the combination did not increase pCR rates; 40.9% for TCHP versus 46.1% for TCHP with estrogen deprivation (p= 0.369) [20].

In parallel another phase II trial (WSG-ADAPT HER2+/HR+) presented in San Antonio Breast Cancer Symposium 2015, compares T-DM1, with or without endocrine therapy versus trastuzumab and endocrine therapy in triple positive early breast cancer. The primary objective was pCR and the secondary objectives were: EFS, OS, toxicity, and safety. After 12 weeks of treatment the pCR rate was no different between T-DM1 plus endocrine therapy (45.8%) and T-DM (40.5%). T-DM1 with or without endocrine therapy was better than trastuzumab plus endocrine therapy (pCR: 15.1%, p<0.001) [21]. Therefore, despite the low toxicity, the addition of endocrine therapy did not show any benefits in pCR in either of the two aforementioned studies.

Due to good tolerability profile of the last mentioned trial, development of the tumor during pregnancy, a relationship with hormone levels, no response to standard neoadjuvant treatment, activity of T-DM1 following to pertuzumab and after discussing extensively with the patient, she agreed to receive the above mentioned treatment, T-DM1 and endocrine therapy, with an impressive response and low toxicity: asthenia grade 1 and hot flushing grade 2. In our opinion, the excellent response obtained is probably related to hormonal treatment because of the development of the tumor during the pregnancy. After reaching pCR her probability to be alive at 5 years was better than we thought at first. Today, 40 months later she is free of disease and she has returned to work.

Sometimes alternative treatment regimens, if we can identify the patients adequately, can contribute to improvement in their prognosis. The hope for the future is achieving more pCR and avoiding toxicity thanks to better selection of patients.

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