Early-onset Brain Metastases in a Breast Cancer Patient after Pathological Complete Response to Neoadjuvant Chemotherapy

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Abstract. Breast cancer patients who achieve a pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) usually have a favourable prognosis. We report on a patient with early metastases to the brain after achieving pCR. The primary tumour was 7.0 cm in diameter with axillary lymph node metastases, hormone receptor-negative, human epidermal growth factor receptor-2-positive (3+), and histological grade 2 with 60% of cells positive for Ki-67. The patient underwent NAC followed by surgery, and achieved pCR. Five months after surgery, during adjuvant treatment with trastuzumab, she developed headache and dizziness. Brain imaging revealed multiple metastatic brain tumours. She received whole-brain radiotherapy followed by lapatinib and capecitabine therapy. At 7 months after surgery, she remains alive with a persistent mild headache. Physicians should be aware of the possibility of early brain metastases, and consider new treatment strategies to prevent brain metastases in high-risk patients who achieve pCR.

The standard-of-care for locally advanced breast cancer includes neoadjuvant chemotherapy (NAC). The response to NAC, in particular the achievement of a pathological complete response (pCR), is used as a marker of the efficacy of treatment as well as a prediction of outcome. Recently, several studies report that breast cancer patients who achieved pCR after NAC had better overall and disease-free survival than those who did not achieve pCR, especially human epidermal growth factor receptor-2 (HER-2)-positive and triple-negative patients; and that pCR of the axillary lymph nodes was an excellent prognostic factor for locally advanced breast cancer (1-4). We report on a patient with HER-2-positive invasive breast cancer with axillary lymph node metastases, who achieved pCR for both the main tumour and the axillary lymph nodes after NAC. However, she developed symptomatic multiple brain metastases during adjuvant trastuzumab therapy.

Case Report

A 41-year-old pre-menopausal woman was referred to our hospital with a right breast mass. Physical examination revealed a 6-cm mass in the upper inner region of the right breast. She had palpable axillary lymph nodes, measuring up to 2 cm in diameter. Mammography revealed architectural distortion and focal asymmetric density in the middle inner region of the right breast. Ultrasonography revealed a heterogenous 7-cm diameter breast mass and enlarged axillary lymph nodes. Computed tomography (CT) and magnetic resonance imaging from the neck to the pelvis did not show any distant metastases. Core needle biopsy of the tumour revealed invasive ductal carcinoma of histological grade 2. Immunohistochemical examination was negative for oestrogen and progesterone receptors, and showed positive membrane staining for HER-2 (3+ score) with 60% of cells positive for Ki-67. The tumour was diagnosed as clinical stage T3N2M0, Stage IIIA. According to the National Comprehensive Cancer Network (NCCN) guidelines (5), the patient received NAC.
with 5-fluorouracil (500 mg/m²), epirubicin (100 mg/m²) and cyclophosphamide (600 mg/m²) administered four times every 3 weeks, followed by docetaxel (75 mg/m²) and trastuzumab (induction dose: 4 mg/kg, maintenance dose: 2 mg/kg) administered four times every 3 weeks. After NAC, only induration of the right breast was apparent on physical examination, and only a scar with low echogenicity was observed on ultrasonography. No enhanced lesions were observed in the right breast or axillary lymph nodes on CT or magnetic resonance imaging. Serum tumour marker levels (carcinoembryonic antigen and carbohydrate antigen 15-3) were within normal limits before and after chemotherapy. The patient subsequently underwent quadrantectomy of the right breast and axillary lymph node dissection. Postoperative pathological examination of the resected breast tissue revealed no invasive carcinoma except for a very small ductal component. Examination of the resected lymph nodes showed fibrotic changes, indicating disappearance of the axillary lymph node metastases. According to the Texas M.D. Anderson Cancer Center criteria, the response to NAC was categorized as pCR (ypT0/is, ypN0), which indicates complete disappearance of invasive carcinoma in both the breast and axillary lymph nodes, but can include residual ductal carcinoma-in-situ (6). The patient received postoperative adjuvant trastuzumab therapy. Five months after surgery, she complained of severe headache and dizziness. Contrast-enhanced CT of the brain revealed metastatic lesions in the right and left cerebrum and right cerebellum, with surrounding edema (Figure 1). Whole-brain radiotherapy (WBRT) was performed immediately (total dose of 37.5 Gy in 15 fractions), followed by combination therapy with lapatinib and capecitabine. Currently, at 7 months after surgery, she is alive with a persistent mild headache.

Discussion

We present a patient in whom achievement of pCR did not predict the outcome in terms of central nervous system (CNS) metastases. Several studies have identified risk factors for brain metastasis in patients with breast cancer, including young age, large tumour size, lack of response to hormone therapy, and overexpression of HER-2 (7-10). It is possible that our patient had CNS metastases at the time of diagnosis. As most drugs, trastuzumab cannot cross the blood-brain barrier due to its molecular weight and hydrophilic properties (11-14). Lapatinib is another HER-2-targeted agent used in the treatment of breast cancer. Lapatinib differs from trastuzumab in that it is a reversible tyrosine kinase inhibitor designed to target both HER-1 and HER-2. Because it is a small molecule (MW <1 kDa), it can theoretically cross the blood-brain barrier and treat CNS metastases. A pre-clinical study showed that 14C-lapatinib was able to penetrate brain metastases from breast cancer in immunocompromised mice (15). Recently, a phase II study was conducted to evaluate the usefulness of first-line combination therapy with lapatinib and capecitabine for avoiding or delaying WBRT in patients with HER2-positive breast cancer and brain metastases (16). Further research of agents that can penetrate the CNS is needed.

Figure 1. Multiple metastatic tumours (white arrows) with surrounding edema were observed in the right and left cerebrum and right cerebellum.
Conclusion

Achievement of pCR after NAC results in a favourable outcome in most cases of breast cancer, but may not always predict future CNS recurrence. Awareness should be increased regarding the possibility of early brain metastases, even after achievement of pCR. New treatment strategies that could prevent CNS metastases should be considered for patients who achieved pCR but have risk factors such as young age, large tumour size, lack of hormone receptors, and overexpression of HER-2. Further investigation is also required to accurately identify the candidates for radical surgery who are likely to have CNS metastasis.

Conflicts of Interest

The Authors declare that they have no competing interests.

References