Successful Neoadjuvant Therapy with Trastuzumab, Paclitaxel and Epirubicin for an Elderly Patient with Inflammatory Breast Cancer

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Abstract. A 75-year old woman presented with diffuse left breast enlargement, redness, edema, and a firm palpable lymph node with skin fixation in the left axilla. The tumor was diagnosed as invasive ductal carcinoma with a strongly positive human epidermal growth factor receptor 2 (HER2) score (3+). She was diagnosed as having inflammatory breast cancer (IBC) (T4d N2M0, stage IIIb). The patient received primary systemic chemotherapy with 4 courses of epirubicin 75 mg/m² and cyclophosphamide 500 mg/m² every three weeks, then 12 courses of paclitaxel 80 mg/m² and trastuzumab 2 mg/kg (initially 4 mg/kg) weekly. Six months after the start of chemotherapy, a left modified radical mastectomy with axillary dissection was performed. No cancer cells in the breast specimen and no metastases to the axillary nodes were observed, so the therapeutic effect was determined as a pathological complete response (pCR). This report suggests that combination therapy with epirubicin and cyclophosphamide followed by trastuzumab and paclitaxel was useful for HER2-positive IBC.

Inflammatory breast cancer (IBC) is a relatively rare disease, accounting for 0.88% of all breast carcinomas, according to the report of a questionnaire survey in Japan (1). In contrast IBC accounts for approximately 2% of all breast malignancies in the USA (2). The prognosis of this disease is poor, Hance et al. reported that the median survival of women with IBC (2.9 years) was statistically significantly shorter than that of women with non-inflammatory locally advanced breast cancer (6.4 years; p<0.0001) (2). The current consensus treatment is multimodal, a first-line chemotherapy with an anthracycline-based regimen with a taxane followed by mastectomy and axillary dissection for responders, locoregional radiotherapy and hormone therapy (3, 4). In addition, trastuzumab treatment has become a standard of care for human epidermal growth factor receptor 2 (HER2)-positive breast carcinomas. HER2 is overexpressed in 25% of breast carcinomas (5), and several studies have shown higher relapse and mortality rates in HER2-positive breast carcinomas. Trastuzumab is a humanized monoclonal antibody directed against the extracellular domain of HER2 (6). Trastuzumab as a single agent or in combination with standard chemotherapy has demonstrated a favorable outcome for metastatic breast cancer overexpressing HER2 (7-9). The addition of trastuzumab to chemotherapy in the neoadjuvant setting could significantly increase the pathological complete response (pCR) rate in patients with HER2 positive breast cancer (10).

Here, a case of HER2-positive IBC is described in which pCR resulting from treatment treated with epirubicin and cyclophosphamide followed by trastuzumab plus paclitaxel.

Case Report

A 75-year old woman noticed a tumor in the left breast in May, 2006. The mass was hard, 20×20 mm in size and located in the sub-areola of the left breast. She presented with diffuse left breast enlargement, redness and edema. A firm lymph node with skin fixation was palpable in the left axilla. A mammogram revealed skin and trabecular thickening, poor extension of the left breast, and no mass. Ultrasound revealed a low echoic mass of 20 mm in diameter under the left areola, marked skin edema, and swollen axillary lymph nodes with fixation to each other. Enhanced computed tomography (CT) of the chest and upper abdomen revealed marked skin...
thickening and parenchymal edema of the left breast on irregular shaped mass under the left areola, axillary lymph node metastases and no distant metastases (Figure 1). A core needle biopsy of the tumor was performed and invasive ductal carcinoma was diagnosed pathologically (Figure 2a). In addition, immunohistochemical analysis revealed that the tumor was estrogen receptor positive, progesterone receptor negative and the HER2 score was strongly positive (3+) (Figure 2b). Although dermal lymph emboli on skin biopsy were not identified pathologically, a few suspicious cells in the lymph vessel were recognized (Figure 2c, 2d). Fine-needle aspiration cytology of the swollen axillary lymph node revealed adenocarcinoma. The patient was diagnosed as having clinically secondary IBC (T4d N2M0, stageⅢb).

In June 2006, the patient began to receive primary systemic chemotherapy with 4 courses of epirubicin 90 mg/m² and cyclophosphamide 500 mg/m² every three weeks, then 12 courses of paclitaxel 80 mg/m² and trastuzumab 2 mg/kg (initially 4 mg/kg) weekly. Five days after the initial chemotherapy, severe vomiting and diarrhea of grade 3 (based on the National Cancer Institute, Common Terminology Criteria for Adverse Events, version 3.0 (11)) were observed, epirubicin 75 mg/m² and cyclophosphamide 500 mg/m² were administered in the following courses. No other severe adverse events were observed during the treatment period except for grade 3 leukopenia and grade 3 neutropenia. Echocardiography to assess the left ventricular ejection fraction (LVEF) was performed before and after treatment the initial LVEF was 72% and after treatment it was 75%. Six months after the start of chemotherapy, enhanced CT of the chest and upper abdomen was performed, which revealed a CR for the skin thickening, parenchymal edema and mass of the left breast, and the axillary node metastases (Figure 3).

In December 2006, a left modified radical mastectomy with level I-II axillary dissection was performed. No cancer cells in the breast specimen and no metastases to the axillary nodes (0/13) were observed pathologically (Figure 4). Therefore, the therapeutic effect of the neoadjuvant therapy was determined as pCR. The patient refused to receive radiotherapy to the left chest wall and continued trastuzumab therapy after surgery. Exemestane as hormone therapy was taken after surgery. In August 2009, the patient was alive and well without locoregional or distant metastases.

Discussion

The American Joint Committee on Cancer defined IBC as a clinicopathological entity characterized by erythema and edema of the skin of the breast, called peau d’orange, with or without an associated mass (12). The clinical presentation of IBC is due to dermal lymph emboli, which may or may not be present on skin biopsy, but pathological features are not necessary for a diagnosis of IBC. In this case, the skin biopsy before treatment revealed no dermal lymph emboli, but the postchemotherapeutic histology showed a few degenerated cells with large hypertrophic cytoplasm and nuclei in the lymph vessel, therefore suggestive of dermal lymph emboli.

Limited benefit of chemotherapy for IBC in women age 70 years or older has been reported because the multiple randomized clinical trials had an insufficient number of
Figure 2. Microscopic analyses. a: Core needle biopsy specimen, invasive ductal carcinoma with nuclear grade 3 (×200). b: Human epidermal growth factor receptor 2 (HER2) expression by immunohistochemistry, Herceptest™ score strongly positive (3+) (×200). c: Skin biopsy specimen, no cancer cells or dermal lymph emboli identified (×10). d: Inflammatory cells in lymph vessel (arrow) (×200).

Figure 3. Chest multidetector computed tomography (CT) of the patient after the neoadjuvant treatment (December 2006). a: Improvement of the skin thickening and parenchymal edema of the left breast, and disappearance of mass under the left areola. b: Sagittal image through the left chest shows disappearance of axillary lymph node metastases (arrow).
patients age 70 years or older (13). The use of adjuvant chemotherapy on relapse and mortality in older patients is strongly influenced by comorbidity and age, therefore, no standard recommendation can be made (14, 15). The present patient was 75 years old, with an expected poor prognosis. However, she had no comorbidities, therefore she should have been recommended to receive treatment with combination of trastuzumab plus chemotherapy as any younger patient would have been.

Although many studies have reported multimodal treatment of IBC (16), there have been only a few reports regarding HER2-positive IBC treated with trastuzumab. Burstein et al. (17) reported that among six patients with IBC treated with trastuzumab and paclitaxel followed by doxorubicin plus cyclophosphamide as preoperative therapy, no pCRs were observed. Asakura et al. (18) reported that a patient diagnosed as IBC was treated with trastuzumab plus vinorelbine, and the clinical response to the therapy was judged as a complete response, but this was not confirmed pathologically. On the other hand Buzdar et al. (10) reported that the pCR rate in the neoadjuvant setting was 65% for patients treated with trastuzumab plus chemotherapy compared to 26% for patients treated chemotherapy alone in stage II to IIIA disease.

Additionally, pCR has been shown to predict improved disease-free and overall survival when compared with patients with non-pCR (19, 20). Therefore the goal of multimodal treatment for IBC should be pCR and trastuzumab is essential for treating patients with HER2-positive IBC. Fortunately in the present patient, the clinical and pathological responses to the multimodal therapy were complete and she was alive and well without locoregional or distant metastases more than 2 years 8 months after surgery. Although further follow-up of this patient will be necessary for prognosis, the result suggests that the subset of patients with HER2-positive IBC would have great benefit from
trastuzumab-based chemotherapy. Careful management for this combined therapy or evaluation of comorbidities in elderly patients will be necessary.

References


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