Case 16-2012: A 32-Year-Old Woman with HER2-Positive Breast Cancer

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of activity in the right axilla, thought to represent metastases to lymph nodes. There was also a subtle focus of increased metabolic activity involving the tip of the left scapula. The patient came to the cancer center at this hospital for advice regarding treatment.

The patient reported no weight loss, fever, fatigue, headache, changes in vision, nipple discharge, breast or chest pain, erythema, or shortness of breath. Menarche had occurred at age 11 years; she was currently menstruating. She had taken oral contraceptives for 3 to 4 years in the past, and depot medroxyprogesterone acetate had been administered intermittently for less than 4 years. Her first full-term pregnancy occurred when she was 23 years of age and was complicated by idiopathic thrombocytopenia; she had had two cesarean sections and had three children. She had a history of endometriosis and had had several orthopedic procedures. Medications included carbamazepine, calcium, and vitamins. She had no known allergies. She lived with her husband and children (the youngest was 14 months of age) and did not work outside the home. She drank alcohol in moderation and did not smoke. Three maternal relatives had had breast cancer — a maternal second cousin when in her 40s and two maternal great-aunts (one when in her 60s). Her paternal grandfather had lung cancer at 85 years of age, and her paternal grandmother had colon cancer.

On examination, the vital signs were normal and the body-mass index (the weight in kilograms divided by the square of the height in meters) was 20.7. There was a mass, 6 to 7 cm in diameter, in the upper outer quadrant of the right breast that extended subareolarly, and the overlying skin had peau d’orange changes, without erythema. There was no bone tenderness, including in the left scapula, and the remainder of the examination was normal. The white-cell count was 3800 per cubic millimeter (reference range, 4500 to 11,000); the rest of the complete blood count and differential count were normal, as were the blood levels of electrolytes, glucose, total protein, albumin, and globulin and tests of renal and liver function. The next day, a bone scan performed at the other hospital showed no evidence of metastatic disease. Results of transthoracic echocardiography were normal. Management decisions were made.

**Differential Diagnosis**

Dr. José Baselga: May we review the imaging studies?

Dr. Elizabeth A. Rafferty: The mammogram showed a spiculated mass in the upper outer quadrant of the right breast that corresponded to the palpable abnormality. Ultrasound examination of the corresponding region of the breast showed an irregular hypoechoic mass, 2.2 cm in maximal dimension, with posterior acoustic shadowing and some associated skin thickening. These mammographic and ultrasonographic results were highly suspicious for cancer.

A breast MRI was performed. The patient’s lactational state caused extensive background enhancement; however, there were two spiculated, enhancing masses at the 10 o’clock axis of the right breast (Fig. 1A). The more posterior mass, corresponding to the palpable lump, was approximately 2 cm in greatest dimension. The more anterior mass, previously unsuspected, was 1.8 cm. Its presence was confirmed with ultrasonography, and a biopsy specimen was obtained with ultrasound guidance.

**Pathological Discussion**

Dr. Alessandro Bombonati: Examination of the initial biopsy specimen of the mass from the right breast revealed invasive ductal carcinoma, grade 3 of 3, spanning at least 1.0 cm. A small focus of high-grade ductal carcinoma in situ involving a few ducts was also present. No lymphatic or blood-vessel invasion was identified (Fig. 2A and 2B). Immunohistochemical staining showed that the tumor cells were negative for both estrogen-receptor and progesterone-receptor proteins and there was strong (3+) overexpression of HER2 (Fig. 2C).
Dr. Rafferty: A CT scan of the abdomen (Fig. 1B) showed multiple liver lesions, at least eight in the right lobe, the largest of which was 1.6 cm in diameter, and a single lesion in the left lobe. The lesions were consistent with hepatic metastases.

**DISCUSSION OF MANAGEMENT**

Dr. Baselga: This young woman has a locally advanced, HER2-positive breast cancer with probable metastatic disease to the liver. This case illustrates a number of issues that clinicians face in the care of patients with metastatic breast cancer and of patients with HER2-positive tumors. HER2, a proto-oncogene encoding the HER2 tyrosine kinase receptor, is amplified in 15 to 20% of patients with breast cancer, resulting in HER2-receptor overexpression and an aggressive clinical phenotype associated with high metastatic potential and shortened survival. Fortunately, during the past decade, the outcome of patients with HER2-positive breast cancer has markedly improved with the advent of molecular targeting of the HER2 receptor with the humanized monoclonal antibody trastuzumab (Herceptin, Genentech). Since the benefit of trastuzumab therapy is strictly limited to HER2-positive breast cancer, the HER2 status is now tested in every patient with newly diagnosed breast cancer. A joint guideline by the American Society of Clinical Oncology and the College of American Pathologists recommends that the determination of HER2 positivity by either immunohistochemical analysis or fluorescence in situ hybridization (FISH) be carried out only in vali-
In this case, the tumor was found to be positive by immunohistochemical analysis, as defined by uniform, intense membrane staining in more than 30% of invasive cells. Since HER2 status was determined in a validated laboratory, performing FISH would not have been of additional value.

Another initial consideration in this case is whether the patient's physicians should obtain histologic confirmation of metastatic disease in the liver. Accurate assessment of the presence of metastatic disease in patients with breast cancer is critically important, since the presence of metastatic disease converts a potentially curable cancer to a incurable disease and is associated with substantially different treatment goals. Histologic confirmation of metastatic disease should be strongly considered in some cases, such as those in which there are a small number of potentially metastatic lesions, the lesions are in an unusual site, or the primary tumor has a low inherent risk of metastasis. However, in my opinion, there is little question that this patient had metastatic disease, since she presented with at least eight space-occupying lesions in the liver and such metastases are commonly associated with HER2-positive breast cancers. However, in the unlikely event of a dissociated response to therapy between the primary tumor and the liver lesions, a liver biopsy should be considered at that time.

Trastuzumab will be the backbone of therapy for this patient with metastatic HER2-positive breast cancer. Although trastuzumab administered as a single agent has antitumor activity, the...
highest clinical benefit is observed when trastuzumab is given in combination with chemotherapy. Multiple agents in combination with trastuzumab have shown clinical activity. However, the only randomized trials that have shown improved survival are those involving the use of taxanes, and therefore, I would recommend a taxane-containing regimen for this patient. In summary, in this patient with newly diagnosed HER2-positive, hormone-receptor–negative metastatic breast cancer, my choice would be systemic therapy with trastuzumab and a taxane.

Dr. Nancy Lee Harris (Pathology): Dr. Younger, would you tell us how you treated this patient?

Dr. W. Jerry Younger (Hematology–Oncology): Because of published data suggesting the efficacy of carboplatin in addition to taxanes and trastuzumab, we chose to treat the patient with carboplatin, docetaxel, and trastuzumab, administered at 3-week intervals. After two cycles, we were pleased that on physical examination it was difficult to feel the mass and the skin changes had subsided. After four cycles, imaging studies showed complete resolution of all disease in the liver. The axillary disease had also resolved. The patient received a total of eight cycles of treatment and then continued trastuzumab as monotherapy. One year after the initiation of treatment, we repeated the imaging studies.

Dr. Baselga: In this patient, therapy consisted of a combination of carboplatin, docetaxel, and trastuzumab. Although both preclinical studies and phase 2 clinical trials, as well as a subset analysis of a small phase 3 study, suggested a synergistic effect with the combination of platinum derivatives and trastuzumab, a recent and larger phase 3 study has shown that the addition of carboplatin to taxanes and trastuzumab may result in more toxic effects and no improvement in any efficacy end points. The results of this study also remind us that new combination therapies should be shown to be superior in randomized clinical trials before they are implemented in daily clinical practice.

Dr. Rafferty: On restaging examinations a year after the initiation of treatment, an abdominal CT scan showed resolution of all the hepatic lesions, with the exception of the single lesion in the left lobe (Fig. 1D). To further characterize the hepatic mass in the left lobe, an MRI was obtained and showed the lesion to be hypointense on T1-weighted images, hyperintense on T2-weighted images, and nonenhancing, features consistent with a simple cyst.

A repeat mammogram showed extensive pleomorphic calcifications associated with a vague mass involving most of the upper outer quadrant of the right breast. Ultrasound examination at the 10 o’clock position showed a small residual mass. Breast MRI (Fig. 1C) showed an irregular area of enhancement, up to 5.4 cm in greatest dimension, extending from the upper outer quadrant to the upper inner quadrant of the right breast. The enhancement on MRI probably reflects a combination of residual tumor and inflammatory response to neoadjuvant therapy.

Dr. Baselga: This patient had a remarkable response to therapy, with complete remission of disease in all known metastatic sites. Although an overall response of HER2-positive metastatic disease to first-line therapy occurs in up to 70% of patients, complete remissions, such as the one observed in this patient, are seen in only 7 to 8% of patients. Nonetheless, the remissions can be long-lasting; some patients who participated in the initial clinical trials with trastuzumab are still in remission more than 15 years later. In this patient, the role of local therapy to the primary tumor now has to be considered. Although surgical resection of the primary tumor has traditionally been reserved for symptom palliation, retrospective series suggest a survival benefit associated with removal of the primary tumor in metastatic disease. A case-matched series from this hospital suggests clinical benefit from local therapy in carefully selected patients with metastatic disease. This patient clearly belongs in the category of patients who are likely to benefit from local therapy.

Dr. Barbara Lynn Smith: This patient’s cytotoxic chemotherapy and trastuzumab treatment resulted in complete resolution of her liver metastases, according to imaging studies; the response was maintained for more than 12 months. Despite the response at the sites of metastatic disease, she had residual disease in her right breast. On clinical examination, she had a 2-cm suspicious mass in the right breast; imaging studies revealed an even more extensive area of concern. In the past, surgery was rarely performed for patients such as this one with metastatic disease, largely because of concern that recuperation or disfigurement from surgery created an excessive burden when life expectancy was short. Surgery was generally
reserved for palliation of symptoms caused by large primary tumors that did not respond to systemic therapy. However, the median survival for patients with metastatic breast cancer is now 12 to 42 months, because of improved therapies and earlier identification of metastatic disease. Furthermore, during the past decade, retrospective studies have suggested a survival benefit among patients with stage IV breast cancer who underwent resection of the primary tumor. A case-control study from this hospital suggests that the observed survival benefit results from selection bias, with surgery preferentially performed in patients with a better prognosis, including those with fewer metastases and those who had a previous response to systemic therapy.

In thinking about the role of surgery in this patient, we recognized that survival in stage IV breast cancers is linked to the pattern and extent of metastases and to the biology of the tumor. Median survival is shorter in patients, such as this one, who have visceral metastases than in those who have bone-only metastases. However, this patient has a HER2-positive tumor, which means that prolonged therapy with trastuzumab could control tumor progression while allowing a good quality of life during treatment. In patients in whom systemic therapies effectively control metastatic disease and are associated with acceptable adverse-event rates, it is increasingly common to see progression of the primary tumor within the breast. In some cases, the primary tumor becomes the main source of the patient’s symptoms, requiring reconsideration of surgery. Surgical resection of the primary tumor is often preferable to the addition of more toxic systemic therapies and provides more reliable local control.

In this patient, we were concerned that single-agent trastuzumab therapy would not prevent progression of the tumor in her breast. She was young, with an excellent performance status, and was likely to have a sufficient survival benefit such that local control would be relevant. We also hoped to avoid additional cytotoxic chemotherapy for as long as possible. For that reason, we performed a mastectomy of the right breast and immediate breast reconstruction.

**Pathological Discussion**

Dr. Bombonati: Gross examination of the mastectomy specimen, obtained after neoadjuvant chemotherapy and 14 months after the initial biopsy, showed a dominant mass (6.0 cm in greatest dimension) and two adjacent poorly defined masses (1.8 cm and 0.6 cm in greatest dimensions) in the upper outer quadrant. Histologic examination showed foci of residual invasive ductal carcinoma, grade 3 of 3, spanning an area of at least 2.5 cm on tissue sections (Fig. 3A), as well as extensive ductal carcinoma in situ, grade 3 of 3, with comedonecroasis and calcifications (Fig. 3B). Ductal carcinoma in situ extended to 0.15 cm from the anterior margin in one focus. Ten axillary lymph nodes were negative for carcinoma. Additional histologic findings included loose fibrohistiocytic stromal changes that were consistent with a tumor bed chemotherapeutic effect (Fig. 3C) and an area of fibrosis with hemosiderin deposition and hemosiderin-laden macrophages consistent with a healing biopsy site. No lymphatic or blood-vessel invasion was identified. Repeat immunohistochemical studies for hormone receptors and HER2 confirmed the initial tumor phenotype. FISH performed on formalin-fixed, paraffin-embedded tissue revealed HER2 amplification in tumor cells (Fig. 2D).

**Discussion of Additional Management**

**Dr. Baselga:** Fourteen months after the diagnosis, the patient had no documented residual or recurrent disease. Should she continue trastuzumab treatment, and if so, for how long? The appropriate duration of single-agent trastuzumab maintenance therapy is unknown. The decision to stop trastuzumab therapy, which is mostly devoid of long-term side effects, is not easy in patients who have a response to therapy. However, trastuzumab administration is expensive, with a cost upwards of $40,000 per year. Small series have shown long-term disease-free survival in patients with metastatic disease who have stopped trastuzumab after successful local–regional treatment of the primary tumor. Therefore, it would not be unreasonable to stop the administration of trastuzumab at some point if this patient’s remission continues.

One must keep in mind that relapse occurs in most patients and will most likely occur in this patient. In that case, there would be a number of therapeutic options available to the patient. HER2-positive tumors that recur after the cessation of trastuzumab continue to respond to anti-HER2 therapies, including trastuzumab. Options would...
include resuming the administration of trastuzumab and adding another chemotherapy agent such as capecitabine, the introduction of anti-HER2 small-molecule tyrosine kinase inhibitors in combination with either chemotherapy or trastuzumab itself, or participation in available clinical trials with a second generation of anti-HER2 agents such as anti-HER2 antibody–drug conjugates or inhibitors of HER2 dimerization.

Although the disease may recur in multiple sites, trastuzumab-treated populations have an especially high risk of central nervous system metastasis — more than 30% of the patients in some series. The high rate of metastatic disease to the brain is probably due to the high invasive and metastatic potential of HER2-positive breast cancer, together with the limited penetration of trastuzumab across the blood–brain barrier. We are unaware of any data that support early screening, despite the high risk of brain metastasis. In a small study involving MRI screening of the brain in 80 patients with HER2-positive disease that had metastasized elsewhere, asymptomatic brain metastases were detected in 36% of the patients. Although these patients were treated with whole-brain radiation therapy, survival was not prolonged. After receiving whole-brain radiation, patients with HER2-positive brain metastasis have a survival advantage over patients with HER2-negative disease who also received whole-brain radiation. This may be an indication that HER2-positive tumors may have enhanced sensitivity to radiation therapy. On balance, I would not screen this patient (by performing imaging stud-

Figure 3. Right Mastectomy Specimen.
The residual high-grade invasive ductal carcinoma seen in the mastectomy specimen is in the form of single cells and cell clusters (Panel A, hematoxylin and eosin). Residual foci of high-grade ductal carcinoma in situ with comedonecrosis and calcification are seen (Panel B, hematoxylin and eosin). The tumor bed shows the chemotherapeutic effect, including loose fibrohistiocytic stroma and scattered inflammatory cells (Panel C, hematoxylin and eosin). Panel D (fluorescence in situ hybridization) shows amplification of HER2 in the tumor cells.
ies) for the presence of brain metastases, but I would be clinically vigilant and would order imaging studies if neurologic abnormalities appear.

Dr. Younger: We have continued trastuzumab monotherapy. It has now been 1.5 years since the mastectomy and 2.5 years since diagnosis, and the patient has no evidence of recurrence of the disease. We are not screening the central nervous system, but an MRI scan of the brain, obtained because of transient neurologic symptoms, was negative.

Dr. Harris: Are there any questions?

Dr. William U. Shipley (Radiation Oncology): Would you be interested in using sequential analysis of circulating tumor cells to decide possible subsequent therapy?

Dr. Baselga: We now have the capacity to detect the presence of circulating tumor cells in patients with HER2-positive breast cancer. The next steps will be to monitor the presence of circulating tumor cells and, more important, to be able to "interrogate" these cells for potential mechanisms of resistance and to determine their sensitivity to different HER2-targeted therapies.

Dr. Harris: How does trastuzumab enhance the cardiotoxic effects of anthracyclines?

Dr. Baselga: The heart depends on HER2 signaling to recover from a number of insults, including the cardiotoxic effects induced by anthracyclines. Therapy with trastuzumab prevents HER2 from signaling appropriately in the heart and may be responsible for the enhanced cardiac toxic effects observed when anthracyclines are given in combination with trastuzumab.

Dr. Isakoff: Would you consider prophylactic cranial irradiation to reduce the risk of recurrence in the brain?

Dr. Baselga: That is the subject of considerable debate. One has to weigh the potential long-term side effects of prophylactic whole-brain irradiation, including cognitive impairment, in a patient such as this one who has a potentially long survival. In addition, we do not have any evidence that prophylactic total-brain irradiation improves survival or even quality of life. To address this question, we would need to conduct a randomized, clinical trial, but this would be challenging for a number of reasons. Therefore, I would not recommend prophylactic brain irradiation for this patient.

ANATOMICAL DIAGNOSIS

Infiltrating ductal carcinoma of the breast, HER2-positive, with metastases to the liver.

Presented at Massachusetts General Hospital Cancer Center Grand Rounds.

Dr. Baselga reports receiving payment for board membership from Chugai; consulting fees from Bayer, Chugai, Exelixis, Roche Genentech, Merck, Novartis, Onyx, Sanofi Aventis, Sea Lane Biotech, and Verastem; consulting fees to his institution from GlaxoSmithKline; and payment to his institution for clinical-study-report review from Merck. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Dr. Bombonati is currently at the Department of Pathology, Thomas Jefferson University Hospital, Philadelphia. We thank Dr. Dror Michaelson for helping to organize the conference.

REFERENCES

10. Pegram MD, Pienkowski T, Northfelt DW, et al. Results of two open-label, multicenter phase II studies of docetaxel,

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