HER2-Mutated Breast Cancer Responds to Treatment With Single-Agent Neratinib, a Second-Generation HER2/EGFR Tyrosine Kinase Inhibitor

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Abstract

Activating mutations in the HER2 tyrosine kinase have been identified in human breast cancers that lack *HER2* gene amplification. These patients are not candidates for HER2-targeted drugs under current standards of care, but preclinical data strongly suggest that these patients will benefit from anti-HER2 drugs. This case report describes a young woman with metastatic breast cancer whose tumor was found to carry a *HER2* L755S mutation, which is in the kinase domain of HER2. Treatment with the second-generation HER2/EGFR tyrosine kinase inhibitor neratinib resulted in partial response and dramatic improvement in the patient's functional status. This partial response lasted 11 months, and when the patient's cancer progressed, she was treated with neratinib plus capecitabine and her cancer again responded. This second response parallels the benefit seen with continuing trastuzumab in *HER2*-amplified breast cancer after disease progression. This case represents the first report, to our knowledge, of successful single-agent treatment of *HER2*-mutated breast cancer. Two clinical trials of neratinib for HER2-mutated metastatic breast cancer are currently enrolling patients. Further, data from The Cancer Genome Atlas project have identified *HER2* mutations in a wide range of solid tumors, including bladder, colorectal, and non–small cell lung cancers, suggesting that clinical trials of neratinib or neratinib-based combinations for *HER2*-mutated solid tumors is warranted. (J Natl Compr Canc Netw 2015;13:1061–1064)

Breast cancer genome sequencing has identified *HER2*-activating mutations in cancers that are *HER2*-negative by immunohistochemistry or fluorescence in situ hybridization.[1,2] These HER2-activating mutations cause an oncogenic transformation of breast epithelial cells in tissue culture and increase tumor growth in xenograft models.[2,3] The sensitivity of these HER2-activating mutations to HER2-targeted drugs has been measured,[2,4] and 2 clinical trials are screening patients with metastatic breast cancer for *HER2* mutations, and treating patients with HER2-positive breast cancer with the second-generation HER2/EGFR tyrosine kinase inhibitor neratinib (HKI-272) (ClinicalTrials.gov identifiers: NCT01670877 and NCT01953926). This report describes the first case of a *HER2*-mutated breast cancer that clinically benefited from neratinib monotherapy. When this patient's cancer progressed, she was placed on neratinib plus capecitabine combination therapy and she again experienced response.

Case Presentation

The patient was diagnosed with stage IV invasive ductal carcinoma in 2003. She was 43 years old and presented

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with a 2-cm mass in the left breast and bone metastases. Biopsy demonstrated that this tumor was estrogen receptor (ER)–positive, progesterone receptor (PR)–negative, and HER2-negative by immunohistochemistry. Her family history was negative for breast and ovarian cancer and her test results were negative for germline mutations of *BRCA1* and *BRCA2*. She was treated with oophorectomy, letrozole, and zoledronic acid, and experienced an excellent clinical and radiologic response. In 2005, a new breast mass was found in the same breast and biopsy results revealed invasive ductal carcinoma that was hormone receptor–negative and HER2-negative on immunohistochemistry. A modified radical mastectomy was performed, and chemotherapy with doxorubicin and cyclophosphamide was administered. Therapy with letrozole and zoledronic acid was also continued. In 2010, liver metastases were diagnosed and changing from letrozole to tamoxifen produced disease stabilization. In May 2011, massive hepatic progression was noted, with obstructive jaundice, ascites, and pleural effusion. Treatment with capecitabine and intensive supportive measures resulted in slow resolution of the jaundice, normalization of liver function tests (LFTs), and decline of tumor markers. The ascites did not resolve and analysis revealed chylous content with no malignant cells, possibly caused by secondary cirrhosis. Treatment with capecitabine was discontinued and fulvestrant, 500 mg every 4 weeks was initiated.

In October 2012, progressive disease was observed with peritoneal and omental metastases, a left adrenal mass, and enlargement of liver metastases. Hormonal treatment was stopped and oral vinorelbine was started, with no response. Liver biopsy results showed metastatic breast cancer that was ER-negative, PR-negative, and HER2-negative on immunohistochemistry, and next-generation sequencing by a Clinical Laboratories Improvement Amendments (CLIA)–certified commercial laboratory (Foundation Medicine, Cambridge, MA) identified a *HER2* L755S mutation, amplifications of the *MDM2* and *MYC* genes, and *APC* I1307K mutation. The *HER2* L755S mutation is an activating mutation located in the tyrosine kinase inhibitor binding site of the HER2 kinase domain. It produces resistance to lapatinib, but in preclinical studies is highly sensitive to neratinib, a second-generation HER2/EGFR tyrosine kinase inhibitor.[2,4] This mutation is different from the *EGFR* gatekeeper mutation T790M, which would be T798M in HER2.[5] *HER2* L755S has been observed in patients who have not received prior lapatinib, and this patient had never been treated with lapatinib.

Her ECOG performance status deteriorated to 3, and she was essentially homebound with massive ascites and profound weakness. Neratinib (240 mg orally daily) was obtained through a compassionate access protocol (with approval of the local and central Institutional Review Board), and was started in April 2013. Within 2 months, her performance status dramatically improved to 1, she was able to resume daily activities, including gardening, and she was able to travel abroad on long trips. Her liver enzymes and tumor markers improved (Figure 1) and a CT scan performed in June 2013 showed a 30% reduction of the left adrenal mass corresponding to a partial response by RECIST criteria 1.0. This response persisted for 11 months. In February 2014, clinical worsening was noted with elevated LFTs and tumor markers, and worsening ascites. Capecitabine (3000 mg daily, days 1–14 of a 21-day cycle) was added. The patient's tumor again responded with significant improvement in LFTs and tumor markers. Treatment with both neratinib monotherapy and neratinib plus capecitabine combination therapy was very well tolerated by the patient. She received diarrhea prophylaxis for the first 3 days (loperamide, 4 mg loading dose followed by 2 mg every 4 hours for 3 days) and was then tapered off loperamide. With this prophylactic regimen, the patient experienced no diarrhea.

Discussion

This patient had a *HER2* L755S mutation and she had a partial response from neratinib monotherapy. This response markedly improved her performance status and quality of life. After 11 months, her cancer progressed and treatment with neratinib plus capecitabine produced another disease response, which is analogous to the benefit seen with continuing trastuzumab after progression in *HER2*-positive (*HER2* gene–amplified) breast cancer.[6] Although a prior case report of *HER2*-mutated, inflammatory breast cancer describes treatment with chemotherapy and HER2-targeted drugs (lapatinib and trastuzumab),[7] this case is the first published report of a patient with *HER2*-mutated

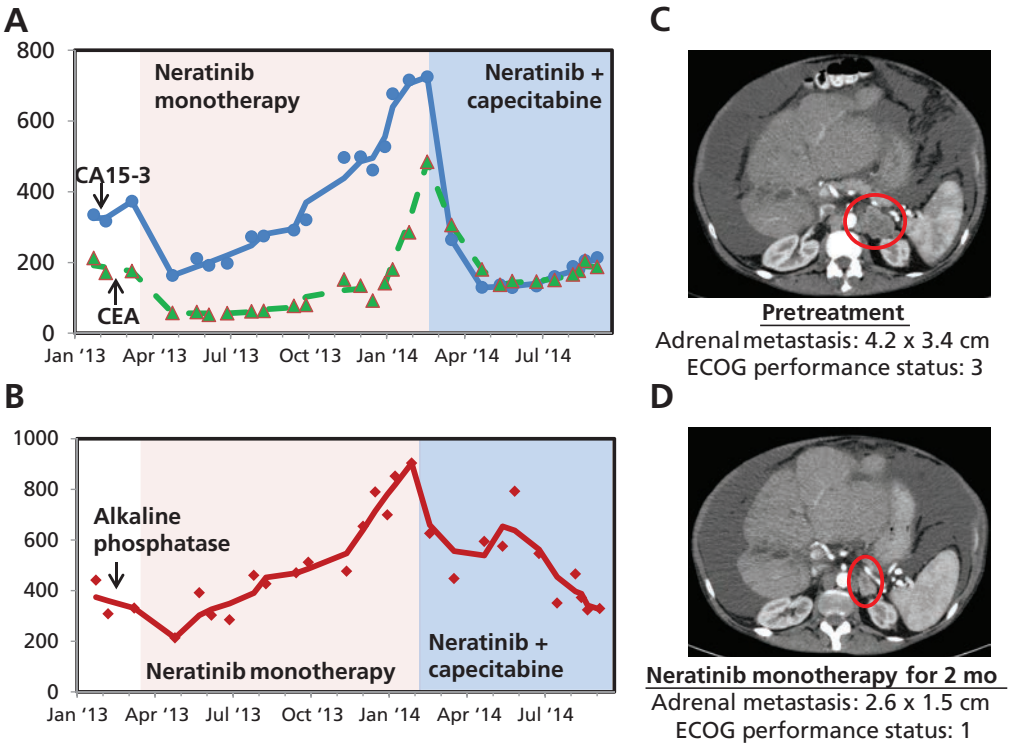

Figure 1 Laboratory and imaging results with neratinib treatment. (A) CA 15-3 (blue) and CEA (green) tumor markers. (B) Alkaline phosphatase values (red). The trend line in both A and B represents a 3-point moving average for the period before neratinib (February–March 2013), on neratinib monotherapy (June 2013–February 2014), and on the neratinib + capecitabine combination (June–September 2014). The time period of neratinib monotherapy and neratinib + capecitabine combination therapy is marked by pink and blue shading, respectively. CA27.29 testing is not routinely available in Israel and no CA27.29 values were available for the patient. (C) CT imaging before neratinib therapy. (D) CT imaging after 2 months of neratinib monotherapy.

breast cancer responding to treatment with a single-agent, HER2-targeted drug. Furthermore, lapatinib would not have been an appropriate drug for our patient, because the *HER2* L755S mutation alters the kinase inhibitor binding site and causes lapatinib resistance.[2,4]

Two clinical trials of neratinib monotherapy for *HER2*-mutated, metastatic breast cancer are currently enrolling patients,[5,6] and trials of neratinib-based combination regimens for *HER2*-mutated breast cancer should be considered in the future. Phase I trials of neratinib with paclitaxel, capecitabine, or vinorelbine have demonstrated that these combinations are safe[8–10]; neratinib has also been combined with other targeted therapy drugs, such as trastuzumab and temsirolimus.[11,12] A phase I trial of a 3-drug, neratinib-containing regimen (neratinib, trastuzumab, and paclitaxel) for *HER2*-positive breast cancer showed good patient tolerability.[13] The main toxicity was diarrhea. With diarrhea prophylaxis, no cases of grade 3/4 diarrhea were observed and grade 2 and 1 diarrhea rates were 17% and 50%, respectively.[13]

The Cancer Genome Atlas project has identified *HER2* mutations in a wide range of solid tumors, including breast, colorectal, bladder, and non–small cell lung cancers.[1,3,14,15] Further, the specific mutations seen in *HER2* are highly recurrent, with the most common mutations occurring either in the kinase domain or at residues 309–310 of the extracellular domain.[2,3] These mutations can be potently inhibited with neratinib,[2] and therefore, investigation of neratinib or neratinib-based combinations for the treatment of multiple solid tumors with HER2 mutations is warranted. Continuation of neratinib in a different drug combination after progression should be considered, because this patient had a second response with the addition of capecitabine to neratinib.

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