A Neu View of Invasive Lobular Breast Cancer

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Running Title: Genomics of Lobular Breast Cancer

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Summary:

Genome sequencing of relapsed, invasive lobular breast cancer identified actionable mutations in 86% of cases. HER2 alterations occur in 27% of cases, including four cases with activating HER2 mutations and one with a novel HER2-GRB7 gene fusion. This fusion links the HER2 tyrosine kinase domain to the GRB7 SH2 domain.

Main Text:

In a recent issue of Clinical Cancer Research, Ross and colleagues performed next-generation sequencing on relapsed, invasive lobular breast cancer using a panel of 182 cancer-related genes. They identified HER2 activating mutations and a HER2 gene fusion in a high percentage of these patients (1). The gene symbol for HER2 is \textit{ERBB2} and alternate names for it include Her2/neu and ErbB-2.

Lobular breast cancer is an uncommon type of breast cancer, accounting for about 10% of breast cancer cases, and it has a significantly lower rate of HER2 gene amplification than invasive ductal breast cancer (2). E-cadherin loss (gene symbol \textit{CDH1}) has been reported in more than 95% of lobular breast cancers (3), and Ross and colleagues use that as a “molecular” eligibility criteria for patients in this study (1). Clinically, lobular breast cancers have an infiltrative growth pattern, and the classical, histopathological appearance shows cells in single-file, producing finger-like strands of invasive tumor cells (Figure 1A). As a result of this infiltrative growth pattern, lobular breast cancer presents with slightly larger tumor sizes than ductal breast cancer and they are more likely to require mastectomy rather than breast conserving surgery (2, 4). Lobular breast cancer also can produce unusual sites of metastasis, such as to the GI tract and the ovary (2, 4). Bone metastases are also common with lobular breast cancer, but lung metastases are less frequently seen. Prior cancer genome sequencing
studies on lobular breast cancers include a Canadian study, which identified 4 cases with HER2 mutations, and The Cancer Genome Atlas (TCGA) Breast Cancer Project, which performed next-generation DNA sequencing on 36 newly diagnosed, lobular breast cancer cases and identified HER2 mutations in 9% of these cases (5, 6).

The clinical and therapeutic importance of HER2 gene amplification in breast cancer has been known for more than 20 years, but the presence of HER2 mutations in breast cancer, independent of HER2 gene amplification has only been recently identified (6, 7). We and others have functionally tested these HER2 mutations and determined that the majority of breast cancer-associated HER2 mutations are activating mutations that increase cellular transformation and tumor formation (7-10). Further, these mutations are sensitive to irreversible, HER2/EGFR tyrosine kinase inhibitors, such as neratinib and afatinib (7, 8). Interestingly, the HER2 mutation L755S produces de novo resistance to the reversible tyrosine kinase inhibitor, lapatinib, and is found in lapatinib-naïve patients, but this mutation can be inhibited in vitro and in cells with low nanomolar doses of neratinib (7, 9). A multi-institutional, phase II clinical trial to screen for HER2 mutations in metastatic breast cancer and to treat mutation positive patients with neratinib is currently enrolling patients.1

In this study, Ross and colleagues identified actionable alterations in 86% of patients, including HER2 alterations in 27% (1). These HER2 alterations included tyrosine kinase domain mutations (L755S, A775_G776insYVMA, P780_Y781insGSP, and V842I), an extracellular domain mutation at a known hotspot (S310F), a novel HER2-GRB7 fusion gene, and 1 case with HER2 amplification. Actionable alterations in other genes include AKT1 E17K mutation (9% of cases), PIK3CA mutations (36% of cases), and FGFR1 amplification (14% of cases). The frequency of HER2 alterations in this study is higher than in prior sequencing studies of lobular breast cancer (5, 6), and this may be due to the focus on relapsed cases or due to the
requirement for E-cadherin (CDH1) mutations as an eligibility criteria. The Cancer Genome Atlas study focused on newly diagnosed patients and reported a 9% frequency of HER2 mutations in lobular breast cancer. If this difference in HER2 mutation frequencies between newly diagnosed and relapsed cases is reproduced by additional studies, then it would suggest that HER2 mutations increase the rate of breast cancer recurrence. This would parallel the increased relapse rate of HER2 gene amplified breast cancers seen in the pre-trastuzumab treatment era (11). It is pertinent to note that while HER2 mutations/gene fusions are enriched in lobular breast cancer in this study (23% in CDH1 mutated, lobular cases compared to 2% in ductal breast cancer cases), they are not exclusive to lobular breast cancer. The authors note that of the 10 breast cancer associated HER2 mutations that they identified in their sequencing studies, half are seen in CDH1 mutant, lobular breast cancer cases and the other half occur in ductal breast cancers (1).

Limitations of this paper include small sample size and lack of functional testing of mutations (1). However, with an uncommon breast cancer subtype, like lobular breast cancer, accumulating a case series with 22 relapsed patients is impressive. While functional studies on many of the actionable mutations have been previously published (7, 8, 12), the effects of the HER2-GRB7 gene fusion have not been tested. This gene fusion combines HER2 exons 1-25 with GRB7 exons 12-15 (Figure 1B). The predicted fusion protein is expected to have intact HER2 extracellular and tyrosine kinase domains and lose more than half of its C-terminal tail sequence, which contains multiple tyrosine autophosphorylation sites. The fusion of the GRB7 SH2 domain would then covalently link a downstream signaling protein to HER2. The functional effect of this is unclear, but the loss of HER2 tyrosine autophosphorylation sites could be mitigated if the fusion protein dimerized and transphosphorylated other EGFR/ERBB family members. Further, the GRB7 SH2 domain could potentially bind to phosphorylation sites in
other EGFR/ERBB family members and thereby increase dimerization and downstream signaling.

There are several clinical implications of this paper. Targeting HER2 mutations with irreversible tyrosine kinase inhibitors is an attractive strategy and a phase II clinical trial using this approach is enrolling patients. Sequencing relapsed, lobular breast cancer patients for HER2 mutations, which will be missed by routine HER2 testing (immunohistochemistry or fluorescence in situ hybridization, FISH) will be important. Next-generation sequencing has the additional advantage of identifying other actionable targets, such as AKT1 or PIK3CA mutations and FGFR1 amplification. Ultimately, however, clinical trials testing the clinical efficacy of genome sequencing and mutation-based assignment of targeted therapies are needed. These trials, which are being planned at multiple institutions and at the national level, offer great potential for the future. Focused sequencing studies such as this study and large scale sequencing studies such as those conducted by TCGA provide a new strategy for targeting breast cancer.

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Footnotes:

1(http://clinicaltrials.gov, NCT01670877).
References


Figure Legend:
Molecular alterations in relapsed, lobular breast cancer. A, Development of lobular breast cancer from normal lobular epithelium of the breast. Loss of CDH1 (E-cadherin) and mutations or gene fusion of HER2 are likely driver events in this process. B, HER2 fusion gene combines exons 1-25 from HER2 with exons 12-15 from GRB7. The predicted fusion protein contains the HER2 extracellular domain (modeled with PDB accession: 1N8Y), HER2 tyrosine kinase model (PDB accession: 3PPO), and the GRB7 SH2 domain (PDB accession: 2QMS).
Figure 1:

A. Luminal epithelium

Myoepithelium

Basement membrane

CDH1 (E—cadherin) loss
ERBB2 mutation or
gene fusion 23%

B. ERBB2 gene fusion

ERBB2 extracellular
domain

Tyr kinase
domain

GRB7 SH2
domain
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