Genomic Analysis of Breast Cancer Heralds a Changing Treatment Paradigm

Presented by Matthew Ellis, MB, BChir, PhD

Deep genomic analysis in breast cancer and the identification of driver mutations will result in treatments based on molecular subtypes and pathways. Mutations not yet familiar to most oncologists will become part of the clinical oncology vernacular. Such discoveries will advance the concept of “biology first, not drug first,” because molecular biology will drive drug development and clinical trial design involving small, molecularly defined subsets of patients, according to a presentation at the NCCN 19th Annual Conference. (J Natl Compr Canc Netw 2014;12:750–752)

“Breast cancer is not one disease, and our molecular terminologies are beginning to have some clinical utility in this regard. For instance, we are able to define a subset [of patients] with very indolent disease, for whom minimal management is appropriate,” he said, “but what our genetic profiles do not yet fully tell us is how to treat high-risk patients. This is where our current efforts should be.”

Deep genomic analysis of breast cancer tumors should soon result in new therapeutic road maps, with treatment paradigms based on a pharmacopeia of cell-type and pathway-matched therapies. Individual cases of breast cancer will ultimately be classified based on a long list of acquired and inherited genetic changes, and appropriate etiology-matched treatment will be based on the identification of driving genetic events in each case, according to Matthew Ellis, MB, BChir, PhD, of Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, St. Louis.

At the NCCN 19th Annual Conference, Dr. Ellis described the molecular subtypes of breast cancer currently part of the oncology vernacular and predicted how some less familiar mutations will eventually become essential to breast cancer management.

Breast Cancer Subtypes and Their Differential Mutations

Next-generation sequencing, which identifies somatic mutations, has shown that estrogen receptor–positive (ER+) and ER– breast cancers are fundamentally different diseases.

“We have made some surprising observations,” Dr. Ellis said. Luminal breast cancers (ER+, HER2–) are marked by a lengthy list of genes that are recurrently mutated. In contrast, triple-negative breast cancers (TNBC)—lacking expression of ER/progesterone receptor (PR), and for HER2 amplification—contain almost no recurrently mutated genes, except for TP53, which is only occasionally mutated in luminal cancers. TNBC overall have more mutations than luminal tumors, so this result is quite confusing.

“There is an alternative process called chromothripsis, in which breast cancers evolve rapidly through multiple chromosomal rearrangements that occur after a single catastrophic cell divi-
sion. A rare cell is able to piece together multiple broken chromosomes and reassemble them into a highly aberrant transformed genome. Theoretically, it appears that luminal A breast cancers conform to the multistep carcinogenesis process; however, more aggressive types of breast cancer (basal-like, luminal B, HER2-enriched), may develop through chromothripsis, which drives more rapid tumor evolution, spelling “bad news for the patient,” he observed.

Those in cancer drug development, he said, have tended to think “drug first, not biology first.” Under this traditional approach, drugs and combinations of drugs are tested on large unselected populations. However, the discovery of HER2 and its targeted agent trastuzumab made clear that first identifying the molecular lesion and then designing the drug to target it meant the need to test fewer patients and that the outcomes of treatment were much greater. HER2 is therefore a wonderful example of “biology first, not drug first.”

“But was HER2 an outlier? Where are the other HER2s?” Dr. Ellis questioned. “Those of us in the research field are scratching our heads. We are deluged with lots of potential HER2s, but also many loss-of-function mutations that are more difficult to drug.”

As the mutational map for luminal-type breast cancer is being elucidated (Figure 1), drugs are being developed that will impact on new targets. Some of these include inhibitors of PI3K, CDK4/6, and MDM2 (which suppressed the expression of p53, a tumor suppressor gene).

Also likely to affect clinical practice, according to Dr. Ellis, is the recognition of HER2 somatic mutations in 2% to 3% of patients who are negative for HER2 overexpression. An ongoing trial is evaluating neratinib, a tyrosine kinase inhibitor, in this population.

Another recent finding is that 10% to 15% of patients who receive multiple endocrine agents develop mutations in the gene for ER (ESR1) that render them resistant to further treatment. Translocations have also been found in the ER, specifically, ESR1/YAP1 fusion, which drives estradiol-independent and fulvestrant-resistant tumor growth.

The effects of the ESR1 mutation may be overcome with high doses of fulvestrant, novel antiestrogens, and other ESR1 inhibitors. “These findings have reignited interest in the endocrine field, and I think we will see drugs that are specific to ESR1-mutated breast cancer,” Dr. Ellis predicted.

**Designing Trials for New Agents**

“We are beginning to stitch all this information together, and it seems we will need a cast of biomarkers

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to tell us who should get which drug,” he added. Clinical trials of new agents will be markedly different from conventional trials because they will use biomarkers.

Dr. Ellis described how these studies would look, based on his own evaluation of neoadjuvant endocrine therapy for ER+ cancer. “We start the endocrine drug, then rebiopsy the patient within a month, and if the tumor is still growing (Ki67 >10%), we triage to a different approach, perhaps chemotherapy. If the tumor is responding with a fall in the Ki67, we keep the patient on neoadjuvant endocrine therapy.”

“During neoadjuvant treatment, we also sequence the tumor, and if a mutation is present, we add a pathway inhibitor. In one trial, for example, we added an AKT inhibitor for patients who had a PIK3CA mutation and a CDK4/6 inhibitor for patients without this mutation,” he said. “Ideally, we would also screen tumors for markers for sensitivity to CDK4/6 inhibitors, like cyclin-D1 amplification. We are trying to learn, on a patient-by-patient basis, what the best recipe should be.”

“This is how breast cancer is going to look: smaller molecularly defined subsets,” he indicated. But since breast cancer is so common, these smaller subsets represent thousands of patients—3% to 4% of breast cancer produces as big a population as chronic myeloid leukemia, a disease in which there have been huge improvements in outcome.

Dr. Ellis acknowledged that many recurrent mutations are not yet actionable in the clinic, but their identification portends well for future treatment. “We are investigating what these abnormalities mean,” he said. “We don’t yet have evidence that you should look for these in practice. We are currently generating a picture of how deep molecular analysis in cancer can promote new therapeutic hypotheses and point to new explanations for why bad things happen.”

“The inescapable conclusion is there is much work to do,” he reiterated, “and my plea is that we need good science. We should not just order expensive panels and then wonder what to do with the results.”

“We are arguing for a systemic approach, and following leads with clinical trials when we understand the biology, we have developed an actionable test where we have done careful experiments to demonstrate how to treat each aberration effectively. By doing this, I believe we definitely will see improvements in patient outcomes in the near future.”