Liquid biopsy testing in monitoring TNBC

By Paul Y. Song, MD

Of all the subtypes of breast cancer, the one patients and physicians fear most is triple negative breast cancer (TNBC). This cancer does not express estrogen, progesterone, or HER-2 receptors and therefore cannot be treated with any existing targeted therapies. TNBC represents less than 20 percent of the quarter-million new breast cancer cases seen in the United States each year, but it is considered the most aggressive, with lower five-year survival rates than most forms of breast cancer and high rates of metastatic disease.

There is currently no known tumor marker or effective means to monitor TNBC patients post-treatment. As a result, physicians can detect recurrence only once it is already clinically present, many times in vital visceral organs, which portends a very poor prognosis. Patients and doctors alike desperately need better detection tools and more personalized information, along with improved therapeutics, to get through this terrifying journey.

Fortunately, there is a promising new approach under investigation that may ultimately lead to earlier detection of recurrence and overall improved outcomes through a more complete utilization of liquid biopsies. It involves implementing a test that measures natural killer cell activity in addition to looking at the markers typically found in liquid biopsies. When taken together, all of this information may provide an effective tool for earlier identification of recurrence and better overall understanding of the current disease situation. This will lead to the identification of new biomarkers and therapeutic targets, and provide a more actionable list of treatment options.

**Liquid biopsy**

In recent years, there has been an explosion of interest in tracking cancer progression through liquid biopsies, or biomarkers found in blood or serum. These tests spare patients the invasive tissue biopsies needed to sample a tumor and allow for much more routine monitoring, and extensive studies indicate that liquid biopsies can pick up signs of recurrence much earlier than standard methods can.

Typically, liquid biopsies are used to look for either circulating tumor cells (CTCs), which are whole cells shed into the bloodstream by a tumor, or circulating tumor cell-free DNA (ctDNA), i.e., fragments of genetic material released as cancer cells undergo apoptosis.

One research team recently published a clinical study of 32 patients with metastatic breast cancer, demonstrating that the combination of CTC and ctDNA data was complementary to information generated with tissue biopsies.1 For two of the most commonly mutated genes in breast cancer, TP53 and PIK3CA, the study showed that CTC and ctDNA data together provided relevant information with 97 percent of the frequency that was obtained in the more invasive tissue biopsy. By performing multiple types of assays and looking at all of this information together—an initial tissue biopsy plus ongoing analyses of CTCs and ctDNA—a much more detailed genomic view over time of cancer activity for TNBC patients can be generated.

Because CTCs and ctDNA are released by different biological processes and reveal separate insights about a patient’s cancer state, analysis of both is complementary rather than redundant. For instance, the real value of CTCs lies in the information they provide on transforming cancer treatment and management though the molecular analysis of cancer biomarkers in blood. Cynvenio developed the Concordia LiquidBiopsy NGS-based technology platform, and markets the ClearID and NK Vue tests for cancer monitoring.

**Natural killer cells**

Natural killer cells play a crucial role in our innate immune system and in the prevention of early cancer development. Research spanning decades has demonstrated that impaired natural killer cell activity is associated with increased cancer risk, and incidence has also been shown to decline with tumor progression.

In one breast cancer study, scientists reported that molecular patterns associated with natural killer cells could be used to predict relapse-free survival.2 These cells can be detected and measured in peripheral blood, where their functionality may be especially indicative of a patient’s cancer state.3 A strong association between low natural killer cell activity and the presence of CTCs in patients with metastatic breast cancer has also been reported.4 It is hypothesized that analysis of natural killer cell activity, coupled with liquid biopsy information, will identify patients in the early stages of recurrence and also predict response to certain cancer therapies.

**The Big Picture**

The ultimate measure of any new approach is whether it makes a difference for patients. Unfortunately, recent studies of CTCs—including the highly regarded SWOG S0500 study5 published in 2014—have found that while these promising biomarkers may have excellent prognostic value, so far they have yielded no information that could guide physicians to a specific intervention. If we are going to use liquid biopsy approaches to help change the paradigm of cancer care for triple negative cases, we must find a way to expand beyond genomic data to extract actionable information focused on therapies that are already approved or in clinical trials.

It is expected that generating a more comprehensive view of each patient’s cancer activity, including CTCs, ctDNA, and natural killer cells along with tissue biopsies, will provide insights that have so far eluded scientists looking at just one of these tests. Since cancer is known to be highly heterogeneous, it makes sense that assembling more data will at the very least offer a more representative picture of the variations present in any given patient. The more data we have, the more likely we are to find specific molecular patterns that can give us much-needed answers.

The TNBC community deserves more. These patients need more effective therapy options, and their medical teams need better tools for detecting recurrence and recommending treatments. The first step toward any of that relies on gathering intelligence: collecting information from as many sources as possible, measuring effects, analyzing correlations, and interpreting results.

Ultimately, seeing the Big Picture of each TNBC case may be the pivotal element that finally allows us to deliver real hope and better care for these patients. Researchers and physicians will join forces to help usher in a new era of improved outcomes for patients with this challenging and complex disease.

References available online

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