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Circulating Tumor DNA May Help Predict Recurrence in Patients with Early Triple-Negative Breast Cancer

Study also indicated that a lack of ctDNA may signal improved outcomes for patients

SAN ANTONIO — The presence of circulating tumor DNA (ctDNA) in early-stage triple-negative breast cancer helped predict the risk of recurrence in women who had undergone surgery after neoadjuvant chemotherapy, according to data presented at the 2019 San Antonio Breast Cancer Symposium (SABCS), held Dec. 10–14.

"For patients who have triple-negative breast cancer with residual disease, the risk of recurrence is exceptionally high," said the study's senior author, Bryan P. Schneider, MD, professor of Medicine and Medical and Molecular Genetics at Indiana University School of Medicine. "Novel therapies and technologies are critical, including those that can potentially predict the risk of relapse."

ctDNA, or tumor DNA derived from plasma, is being explored as a way detect cancer, guide treatment, and monitor patients during remission. The presence of ctDNA can signal the presence of cancer.

"If you are a woman with triple-negative breast cancer, after surgery you are in a constant 'watch and wait' scenario, in fear of the cancer coming back," said the study's first author, Milan Radovich, PhD, associate professor of Surgery and Medical and Molecular Genetics at Indiana University School of Medicine. "We know that a significant proportion of these women will have disease relapse after surgery. ctDNA is a powerful tool to be able to predict recurrence and could help us identify the best ways to manage care for women diagnosed with this disease."

Conversely, the authors – researchers in the Indiana University Melvin and Bren Simon Cancer Center and the Vera Bradley Foundation Center for Breast Cancer Research – said that superior outcomes for those who did not have ctDNA could potentially set the stage for clinical studies evaluating the ability to reduce post-surgical treatment for these patients.

In this study, the authors and colleagues analyzed plasma samples that had been collected from patients enrolled in the BRE12-158 clinical trial, which studied genomically directed therapy versus physician's choice of treatment after preoperative chemotherapy in patients with triple-negative breast cancer. The trial enrolled 196 women, and ctDNA was sequenced in 142 patients using the FoundationOne Liquid Test.

Mutated ctDNA was detected in 90 of the patients, representing 63 percent. TP53 was the most commonly mutated gene, followed by others that are commonly associated with breast cancer.

At 17.2 months of follow-up, detection of ctDNA was significantly associated with inferior distant disease-free survival (DDFS). Patients with ctDNA had a median DDFS of 32.5 months, while the patients without ctDNA had not reached the median.

At 24 months, the DDFS probability was 56 percent in ctDNA-positive patients, compared with 81 percent in ctDNA-negative patients. In multivariate analysis, when the researchers controlled for factors including residual cancer burden; tumor size, grade, and stage; age; and race, detection of ctDNA remained independently associated with inferior DDFS. Overall, ctDNA-positive patients were three times as likely to have distant disease recurrence than ctDNA-negative patients.

Detection of ctDNA was also associated with inferior overall survival; ctDNA-positive patients had 4.1 times increased risk of death compared with ctDNA-negative patients.

"This study establishes that triple-negative breast cancer patients who have ctDNA after neoadjuvant therapy have a higher risk of recurrence," Schneider said. "This may set the stage for further clinical trials for these high-risk patients, evaluating novel ways to prevent recurrence."

The authors said a clinical trial expected to begin in 2020 will further examine ctDNA's potential in guiding therapy for those patients who are at high risk of recurrence. They also noted that sequencing technology is developing rapidly, and will likely become more sensitive and more specific over time.

Schneider and Radovich said one limitation of this study is that the follow-up period is still ongoing, so results may change in future analysis.

This study was funded by the Vera Bradley Foundation for Breast Cancer and the Indiana University Grand Challenge Precision Health Initiative. The trial was managed by the Hoosier Cancer Research Network and enrolled at 26 sites across the U.S. The authors declare no conflict of interest.

ABSTRACT

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Detection of circulating tumor DNA (ctDNA) after neoadjuvant chemotherapy is significantly associated with disease recurrence in early-stage triple-negative breast cancer (TNBC): Preplanned correlative results from clinical trial BRE12-158

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Background: A significant proportion of patients with early-stage TNBC are treated with neoadjuvant chemotherapy (NAC). Sequencing of ctDNA after surgery can be used to detect minimal residual disease and predict which patients may experience clinical recurrence. **Methods:** BRE12-158 is a recently completed Phase II clinical trial which randomized earlystage TNBC patients with residual disease after NAC to post-neoadjuvant genomically-directed therapy vs treatment of physician choice. 151 patients had a plasma sample collected at the time of treatment assignment (after surgery and radiation). ctDNA was successfully sequenced in 150 patients. 148 of the 150 sequenced patients had clinical follow-up. Sequencing was performed by Foundation Medicine using the FoundationOne Liquid assay which profiles for 70 commonly mutated oncogenes. Presence of mutated ctDNA was associated with distant disease free survival (DDFS) and overall survival (OS) in univariate analysis using the Log-Rank test, and in multi-variate analysis using Cox proportional hazards model. **Results:** Mutated ctDNA was detected in 94 of 148 sequenced patients (64%). TP53 was the most commonly mutated gene consistent with prior genomic studies of TNBC. At 16.7 months of median follow-up, detection of ctDNA was significantly associated with an inferior DDFS (median DDFS 32.5 months vs. Not Reached, p=0.0030). At 24 months, the DDFS probability was 53% in ctDNA-positive patients as compared to 81% in ctDNA-negative patients. In multi-variate analysis, when considering significant covariates, including: residual cancer burden (RCB); number of positive lymph nodes; tumor size; stage; grade; age; and race; detection of ctDNA remained independently associated with inferior DDFS (HR=3.1, CI: 1.4-6.8, p=0.0048). Similarly, detection of ctDNA was associated with inferior OS in univariate (p=0.021) and multivariate analysis (HR=2.7, CI:1.1-6.2, p=0.022). Lastly, we observed a correlation between higher maximum somatic allele frequency and a shorter DDFS interval in multivariate analysis (HR=4.7, CI: 1.04-21.1, p=0.044) and shorter OS (HR=4.9, CI:1.06-22.4, p=0.041), suggesting that the quantitative degree of ctDNA burden is associated with clinical outcome. **Conclusions:** Detection of ctDNA in early-stage TNBC after neoadjuvant chemotherapy is an independent predictor of disease recurrence, and represents an important novel stratification factor for future post-neoadjuvant trials.

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