Serial Circulating Tumor Dna (Ctdna) Assessment To Predict Treatment Response And Identify Genomic Evolution In Patients With Metastatic Breast Cancer (Mbc)

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Abstract

Background:

Next generation sequencing of ctDNA can provide a comprehensive assessment of a tumor's genomic landscape. Serial liquid biopsies enable monitoring for response and resistance. The Individualized Molecular Analysis Guide Efforts in Breast Cancer (IMAGE) II study (NCT02965755) is a prospective, multi-center trial for patients with metastatic breast cancer (mBC) of any subtype planning to initiate a new line of therapy (LOT).

Objective:

We evaluated the clinical utility of serial ctDNA assessment in patients with mBC.

Methods:

Plasma samples from enrollment, 1-2 weeks on next LOT, first restaging, and progression underwent sequencing using FoundationOneLiquid CDx (F1LCDx). ctDNA tumor fraction (TF) was calculated using F1LCDx as a laboratory professional service. Maximum variant allele frequency (maxVAF) was calculated after removing variants with VAF 40-60% or >90% and genes commonly associated with clonal hematopoiesis. We examined TF and maxVAF dynamics vs clinical response at first restaging as extracted from clinical documentation, dichotomized into stable/responding versus progressing. We also evaluated alterations across timepoints.

Results:

Enrollment was 197 patients: 136 ER/PR+/HER2-, 21 HER2+, and 40 ER/PR-/HER2- (193 female, median age: 57 [range 27-86]). Median prior metastatic LOT was 2. At first restaging, 44% of the 84 patients with TF results with a clinical response had a decrease in TF by 90% from baseline, compared to only 9% who progressed (χ-squared p=0.028). A decrease in maxVAF at week 1-2 (n=106 samples) by 90% compared to baseline was not associated with clinical response first restaging (23% vs. 12%, p=0.2715).

5566 alterations were detected in 397 baseline and serial samples. Genes most commonly identified as having emerging pathogenic mutations were DNMT3A (39 alterations), TP53 (26), BRCA2 (22), ATM (20), and PALB2 (18) whereas disappearing pathogenic mutations occurred in TP53 (31), ESR1 (23), PIK3CA (19), PALB2 (14), and BRCA2 (12). Emerging mutations were most often first detected at progression. Disappearing mutations were most often lost at week 1-2.

Conclusions:

Decrease in TF, but not maxVAF, at 1-2 weeks on treatment correlated with clinical response at restaging and may provide an early assessment of treatment response. Genomic evolution was frequently identified by serial liquid biopsies.

Do you have any conflicts of interest?

Yes, I have a conflict of interest.

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