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ASO Author Reflections: The Whole Transcriptome Landscape of Circulating Tumor Cells in Non-Metastatic Breast Cancer

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Past:

Circulating tumor cells (CTCs) have been demonstrated to be prognostic in all stages of breast cancer^{1,2}, yet few clinicians have incorporated them into practice because CTCs did not predict which specific therapy would be effective in treating patients³. The Fisher paradigm contends that operable breast cancer is a systemic disease at its inception and that in addition to proper surgical management, optimal systemic therapy is critical to disease survival outcomes⁴. Previous generations of CTC assays were limited by technical factors relating to the rarity of CTCs, cellular marker expression, lack of blood preservation tubes compatible with downstream assays, and the high cost of next generation sequencing⁵. This study evaluated the hypothesis that it is feasible to isolate and profile CTCs from Stage II-III breast cancer patients prior to receipt of surgery or systemic therapy.⁶ We evaluated known and novel biomarkers using RNA-sequencing to characterize the whole transcriptome of CTCs since not all DNA mutations are expressed.

Present:

CTCs were detected in 88% of stage II-III breast cancer patients using a strategy in which specimen processing began within 20 minutes of blood draw. Our strategy of profiling small pools of ultra-pure CTCs allowed for a quantitative assessment of all detectable transcripts within a specimen. We found that the tumor biology of CTCs was very heterogeneous from patient to patient and that both known and novel biomarkers predictive of treatment response could be identified. When considering a large panel of potentially clinically actionable genes with relevance to breast cancer, few genes showed consistent up-regulation. This suggests that CTCs could be used as a target discovery tool when the biomarkers specific to a given patient's tumor biology are unknown. This further suggests that relatively small panels of biomarker assays such as quantitative real-time PCR or digital droplet PCR for circulating tumor (ct)DNA would only be expected to be informative in the context of the presence of a candidate target.

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Future:

CTCs and ctDNA are examples of liquid biopsies that allow for serial assessment of tumor biology in the context of tumor evolution under the selection pressure of systemic therapy. Liquid biopsies offer the advantage of profiling the diverse repertoire of tumor subclones which may not be present in a single tumor biopsy specimen. Our study demonstrated the feasibility of using liquid biopsy studies to profile rare CTCs even in operable breast cancer patients. This technology could prove beneficial in further studies in which CTCs are used to select treatment targets or for the detection of clinically occult minimal residual disease. This general approach should be further developed with the goal of incorporation into clinical trials – first as observational candidate biomarkers with correlation to trial outcomes in targeted therapy studies. If this approach is validated in clinical trials, CTCs as liquid biopsies could be incorporated into basket trials or platform trials in which biomarkers are used to assign treatment allocation.

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