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Research Perspective

Clinical application of liquid biopsies to detect somatic *BRCA1/2* mutations and guide potential therapeutic intervention for patients with metastatic breast cancer

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ABSTRACT

Plasma based genotyping via cell-free DNA may identify actionable mutations for potential therapeutic intervention in patients with advanced malignancies including breast cancer. In this article, we discuss recent studies using cell-free DNA testing to identify and classify somatic *BRCA1/2* mutations in metastatic breast cancer, and potential future applications for the treatment of metastatic breast cancer.

INTRODUCTION

In recent years, plasma based genotyping via cell-free DNA (cfDNA) or "liquid biopsy" has emerged as a robust means to detect actionable mutations and guide genotype-directed therapies for patients with advanced malignancies [1]. For metastatic breast cancer, the utility of cfDNA in identifying actionable mutations has been demonstrated [2], and recent studies have validated the feasibility of tumor genotyping for targeted treatment matching [3]. Notably, a PI3K inhibitor has now been approved for *PI3KCA* mutant hormone receptor positive (HR+)/HER2- metastatic breast cancer using diagnostic cfDNA testing to identify *PI3KCA* mutations [4]. CfDNA offers the advantage of being less invasive and possibly more sensitive than tumor tissue genotyping assays [5, 6].

PARP inhibitors have recently been approved as a targeted therapy for the treatment of germline *BRCA1/2* mutant metastatic breast cancer based on results from two pivotal phase III clinical trials. The phase III OlympiAD [7] and EMBRACA [8] studies demonstrated significant improvement in progression-free survival with olaparib and talazoparib, respectively, compared to chemotherapy, for metastatic breast cancer. PARP inhibitors may also improve patient reported outcomes and quality of life. However, germline *BRCA1/2* mutations only account for about 5–10% of breast cancer [9], limiting their broad applicability.

A question that arises is whether PARP inhibitors may also be beneficial in metastatic breast cancer with somatic *BRCA1/2* mutations. In a recent study led by our team [10], we demonstrated the emergence of somatic *BRCA1/2* mutations detectable by cfDNA, largely in the absence of germline *BRCA1/2* mutations. In our analysis of 215 patients undergoing cfDNA testing as part of care for metastatic breast cancer, we observed that 29 (13.5%) had somatic *BRCA1/2* mutations detectable in cfDNA, which were seen in various subtypes, and often clonal in nature. Four percent had somatic *BRCA1/2* mutations that were known germline-pathogenic, and the rest were novel variants, based on classification using extrapolation from reputable genomic databases. In addition, we demonstrated increased sensitivity to a PARP inhibitor in a CTC culture derived from a patient with a pathogenic somatic *BRCA1* mutation, highlighting the unique role of PARP inhibition for patients with somatic *BRCA1/2* mutant breast cancer. However, not all somatic *BRCA1/2* mutations are functionally significant, i.e., pathogenic. For example, in a CTC culture derived from a patient with a novel variant *BRCA2* mutation, we did not observe any impact of a PARP inhibitor. Interestingly, this patient also had widespread expression of the APOBEC mutation signature that encompassed the *BRCA2* mutation itself, suggesting the novel *BRCA2* mutation was likely a passenger mutation rather than a driver mutation. Based on these findings, we developed an algorithm to guide clinical assessment of somatic *BRCA1/2* mutations, as well as designed a genotype-directed clinical trial for patients with metastatic breast cancer [11].

A genotype-directed clinical trial is currently ongoing at our institution and other academic centers to determine the efficacy of PARP inhibition in somatic

cfDNA *BRCA1/2*-mutant metastatic breast cancer [11], and the results of this trial may help expand the population of patients who benefit from PARP inhibitors, similar to what has been observed in ovarian cancer. A combined analysis of two studies evaluating a PARP inhibitor in ovarian cancer demonstrated similar efficacy in germline *BRCA1/2* mutant patients and somatic *BRCA1/2* mutant patients [12].

Besides detection of germline and somatic *BRCA1/2* mutations, cfDNA analysis also allows for detection of reversion *BRCA1/2* mutations [13]. The acquisition of *BRCA1/2* reversion mutations is a well described phenomenon [14], which restores the open reading frame (and function) of the *BRCA1/2* gene, thus rendering a PARP inhibitor ineffective. In a second multicenter analysis [13], we demonstrated that routine plasma-based genotyping can be utilized to classify *BRCA1/2* cfDNA mutations as germline, somatic or reversion mutations, based on specific loci and the mutant allele fraction of the *BRCA1/2* mutation. Of 828 patients with advanced malignancies including breast cancer undergoing testing with a 73 gene cfDNA assay, one or more pathogenic *BRCA1/2* mutation was identified in 7.2% of patients, and both somatic and germline variants were detected. Polyclonal reversion mutations were found in 21.4% of patients with germline *BRCA1/2* mutations, most often in association with receipt of a prior PARP inhibitor.

Another study found that the absence of pre-existing cfDNA *BRCA1/2* reversion mutations in patients with ovarian cancer who had somatic or germline *BRCA1/2* mutations and were treated with rucaparib was associated with improved progression-free survival [15]. Therefore, the identification of cfDNA *BRCA1/2* reversion mutations may have important implications for therapeutic response to PARP inhibitors, and will be studied in our ongoing clinical trial of a PARP inhibitor for somatic *BRCA1/2* mutant metastatic breast cancer [11]. A complementary ongoing trial is also evaluating the efficacy of the PARP inhibitor, olaparib, in somatic *BRCA1/2* mutant metastatic breast cancer, with initial results suggesting potential efficacy [16].

In summary, plasma-based genotyping is a promising strategy for the detection of *BRCA1/2* mutations and could potentially guide triage to genotype-directed matched therapy with a PARP inhibitor. Ongoing studies will help determine the therapeutic utility of this approach and impact on long term clinical outcomes for patients with metastatic breast cancer.

Author contributions

All authors contributed to writing this article.

CONFLICTS OF INTEREST

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