Clinical Oncology: Case Reports

Case Report

A SCITECHNOL JOURNAL

A Hereditary Breast and Ovarian Cancer (HBOC) Patient with Metastatic Breast Cancer Lacking BRCA Loss of Heterozygosity (LOH) but Responding to PARP Inhibitor Therapy

Steven Sorscher*

Abstract

A germline (gl) pathogenic BRCA alteration or mutation is the molecular basis for diagnosing an individual with Hereditary Breast and Ovarian Cancer (HBOC) syndrome, the most common inherited breast cancer-predisposing syndrome. The gatekeeper or transforming event almost always involves BRCA Loss of Heterozygosity (LOH), which results in loss of expression of normal BRCA protein.

Recently, the Federal Drug Administration (FDA) approved PARP inhibitor therapy for patients harboring a gl BRCA alteration who have metastatic breast cancer based on a 59.9% response rate of these tumors to PARP inhibitor therapy.

Here, a patient with a gl BRCA pathogenic alteration whose metastatic breast cancer responded to PARP inhibitor therapy is described. However, next-generation sequencing (NGS) liquid biopsy (cell-free (cf) DNA demonstrated no apparent BRCA LOH (the molecular hallmark of BRCA-related breast cancers) and therefore the response of her tumor to the PARP inhibitor would be unexpected. PARP inhibitor therapy would be expected to be effective only if the tumor lacked normal BRCA protein expression, as is seen with BRCA LOH in tumor-derived DNA.

The challenges involved in confirming BRCA LOH based on mutant allelic frequency (MAF) in the cf DNA NGS assay are discussed as well as possible explanations for the demonstrated radiographic response to the PARP inhibitor, despite the apparent lack of BRCA LOH.

Keywords

BRCA; Mutant allelic frequency; Breast cancer; PARP inhibitor

Case Report

A 53-year old woman whose sister developed breast cancer at age 40 underwent a lumpectomy and sentinel lymph node sampling on July 14, 2014, and pathology showed her to have a left-sided 4.5 cm, grade 2 invasive breast cancer with 0/2 Sentinel Lymph Nodes (SLNs) involved with metastatic (Figure 1) disease (overall stage T2N0M0), ER-negative (<1%), PR negative (<1%), HER-2 negative ("0") or triple-negative (TN) breast cancer.

The patient underwent multi-gene panel germline testing which identified heterozygosity for mutated BRCA1 c.815_824dup (p.Thr276Alafs*14) with the report stating "This patient has Hereditary Breast and Ovarian Cancer syndrome" (HBOC). (Myriad Genetics, Inc Salt Lake City, Utah 84108) [1].

She received 4 cycles of dose-dense (dd) adriamycin/cyclophosphamide chemotherapy followed by 4 cycles of dd paclitaxel, completed in November 2014.

In May 2015, she underwent prophylactic Bilateral Salpingo-Oophorectomy (BSO) and pathology revealed no malignancy.

In October 2016, a right breast biopsy showed DCIS (1 cm) with microinvasion. The micro-invasive cancer was TN. She underwent bilateral mastectomies and neither the breast tissue showed residual cancer nor did any of the right-sided 3 SLNs sampled.

In October 2018, a CT chest scan showed 3 lung masses. A percutaneous core needle biopsy was interpreted as "adenocarcinoma" and the pathology report also stated that based on the histology and immunostains the "findings support metastasis from this patient's known breast primary."

On February 8, 2019, she underwent a baseline CT chest/abdomen/pelvis (c/a/p) scan and bone scan and started olaparib therapy (300 mg by mouth, twice daily).

On April 15, 2019, a repeat CT c/a/p reported that the largest of the lung metastases had decreased from 5.4 × 3.8 × 3.1 cm to 5.3 × 2.9 × 3.2 cm and a second metastasis had decreased from 2.7 × 2.0 cm to 2.2 × 1.6 cm and a third (1.3 × 1.6 cm) lung metastasis was unchanged in size. No other lesions were seen on the February 2019 or April 2019 CT scans nor were metastatic disease identified on the bone scan [2].

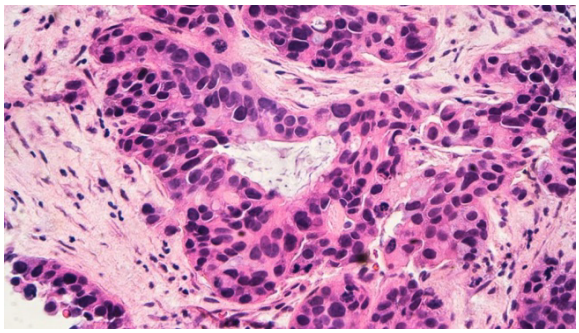

Figure 1: Metastatic breast cancer.

***Corresponding author:** Steven Sorscher, Department of Medicine, Oncology Division, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, U.S.A, NC 27157, Tel: 336-713-1717; E-mail: ssorsche@wakehealth.edu

Received: December 16, 2019 **Accepted:** December 27, 2019 **Published:** January 06, 2020

Repeat scanning continued to show stable or improving disease until a CT c/a/p on 10-30-2019 demonstrated progression of her metastatic breast cancer with the largest lung lesion now measuring 6.9 × 3.5 cm.

An NGS liquid biopsy (cf DNA) demonstrated BRCA1 (T276fs*14) and NRAS Q61Kwith mutant allele frequencies of 53.2% and 3.3% respectively (Foundation Medicine, Inc, Cambridge, MA 02141).

Discussion

The molecular diagnosis of HBOC syndrome is made when an individual is found to have a gl pathogenic BRCA1 or BRCA2 alteration or mutation. Patients who harbor a gl pathogenic BRCA1 alteration are at 60%-80% lifetime risk of developing breast cancer as well as other cancers, including ovarian cancer [3]. As is the case in nearly all other inherited cancer-predisposing syndromes, the inherited pathogenic alteration is in a Tumor Suppressor Gene (TSG) and the gatekeeper or transforming event involves a "second hit" that results in lack of protein expression from the normal, second BRCA allele which, added to the lack of expression of normal protein expression from the inherited pathogenic alteration results in no significant normal TSG protein expression. In the case of an inherited or gl BRCA pathogenic alteration, Osorio demonstrated that lack of normal protein expression of the second allele results from BRCA1 LOH in 93% of cases evaluated [1].

With liquid biopsies, NGS is used to assess for actionable abnormalities identified in the DNA shed from the tumor. Until recently, the MAF for actionable oncogenes or TSGs was not reported with NGS of cf DNA or from the tumor. Since nearly all of the FDA approved available targeted therapies target an oncoprotein expressed from an oncogene, the MAF for an actionable oncogene would not be expected to be predictive of responsiveness to the targeted therapy. However, when a lack of expression of normal protein from both alleles of a TSG would be the biomarker expected to predict response to therapy, the MAF is likely predictive of sensitivity to the targeted therapy. For example, the so-called FDA agnostic approval of the checkpoint inhibitor therapy (pembrolizumab), for any metastatic solid tumor demonstrating deficient protein expression from one of several TSGs (called mismatch repair (MMR) genes), is based on a 40% response rate and high duration of response and underscores this principle [4].

The PARP inhibitor olaparib is FDA approved and National Comprehensive Cancer Center endorsed for treating metastatic breast cancer in patients carrying a gl BRCA pathogenic alteration. The response rate was 59.9% in those patients [2,5]. BRCA1 is a TSG encoding a protein involved in DNA repair. Poly (adenosine diphosphate-ribose) polymerase (PARP) enzymes are also involved in repairing DNA strand breaks. In vitro cells lacking normal BRCA protein expression are sensitive to PARP inhibitors. Therefore the efficacy of olaparib is thought to rely on a lack of normal BRCA expression in the tumor [2,6,7]. However, since 1 of 9 women will develop breast cancer in their lifetime, it is roughly possible that 40% of the non-responding tumors do not respond because their tumors are sporadic and do not in fact lack BRCA expression from the normal BRCA allele, in spite of occurring in a BRCA carrier. Mutated BRCA genes from their tumors would show no LOH and a roughly 50% MAF.

Our patient's metastatic breast cancer responded to olaparib. Her BRCA MAF was reported as 53.2% in her cf DNA. The mutated NRAS MAF was 3.3%. Since essential all of the mutated NRAS DNA would have been derived from the tumor (because NRAS is an oncogene) this implies that the cf DNA from the tumor is roughly 6.6%. Therefore, if there was BRCA LOH the BRCA cf DNA MAF would be expected to be 56.6%, whereas, being a BRCA mutation carrier, the 53.2% BRCA MAF implies that in fact, her cancer was sporadic (i.e. lacked BRCA LOH).

There are several possible explanations for why the described patient's cancer responded to olaparib, despite the calculated cf mutated BRCA DNA from the tumor being 3.2%. For example, it is possible the reported MAF is inaccurate because the percentage of cf DNA assessed from the tumor is quite small relative to the DNA sequences, nearly all of which were derived from normal tissue. It is also possible that the tumor is heterogeneous and a significant portion of cancer actually does have BRCA LOH. It is possible that the lack of protein expression from the second allele results from mechanisms other than BRCA LOH. For example, MMR gene promoter hypermethylation is a common gatekeeper event resulting in deficient MMR (dMMR) protein expression in dMMR Lynch syndrome-related tumors, not MMR LOH [8]. Also, it is possible that a lack of expression from one allele alone (the inherited BRCA pathogenic allele) is sufficient for PARP inhibitor sensitivity. Finally, the liquid biopsy was obtained at recurrence, rather than during the time the tumor was responding to olaparib. It is, therefore, possible that treatment with olaparib led to the selection of surviving clones that had adequate BRCA protein expression (i.e. lacked BRCA LOH) and were therefore resistant to olaparib.

Conclusion

PARP inhibitor therapy is FDA approved for metastatic breast cancer in patients with gl pathogenic BRCA alterations and BRCA LOH is the hallmark of inherited BRCA1 derived tumors. The resulting lack of BRCA protein expression is the presumed mechanism resulting in sensitivity to PARP inhibitor therapy. However, the described HBOC syndrome patient's breast cancer DNA did not show BRCA LOH and yet her cancer responded to the PARP inhibitor. Future studies might include NGS of the tumor or cf DNA from the tumor to determine if patients with gl BRCA pathogenic alterations, but tumor-derived DNA without BRCA LOH, might still respond to PARP inhibitor therapy, as was seen for the patient described in this case report.

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Author Affiliations

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Department of Medicine, Oncology Division, Wake Forest School of Medicine, Medical Center Blvd, U.S.A