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Case Report

EGFR and BRCA2 Mutations in Metastasized Adenocarcinoma of the Lung

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Abstract

A young Asian woman was treated for metastasized adenocarcinoma of the lung. Diagnostic evaluation identified a mutation in the Epidermal Growth Factor Receptor (EGFR) gene as well as a mutation in breast cancer 2 (BRCA2). Response to treatment was seen using radiographic imaging and in plasma Circulating Tumor DNA (ctDNA) levels of the BRCA2 and EGFR mutations.

Case Report

Here we present the case of a 38-year-old never-smoking East Asian woman with metastasized adenocarcinoma of the lung. She harbored an Epidermal Growth Factor Receptor (EGFR) gene mutation (c.2235_2249del p.Glu746_Ala750del) for which she was treated with gefitinib (Iressa®, AstraZeneca, Cambridge, England), a Tyrosine Kinase Inhibitor (TKI), 250 mg OD orally. Although she felt an immediate relieve of symptoms following start of gefitinib, within 2 months there was disease progression. She subsequently received several lines of chemotherapy and immunotherapy with clinical, radiological and serum tumor marker responses during the 2.5 years following diagnosis (Figure 1). Whole genome sequencing was performed on a biopsy from a metastasis and a breast cancer 2 (BRCA2) (c.2095C>T p.Gln699*) truncating mutation was detected (Figure 2). This mutation was confirmed in all other tumor biopsies. She was then started on olaparib (Lynparza®, AstraZeneca, Cambridge, England), a poly (ADP-ribose) polymerase inhibitor (PARPi), 400 mg capsules BID orally, after which a partial response was observed for approximately 2 months (Figure 3).

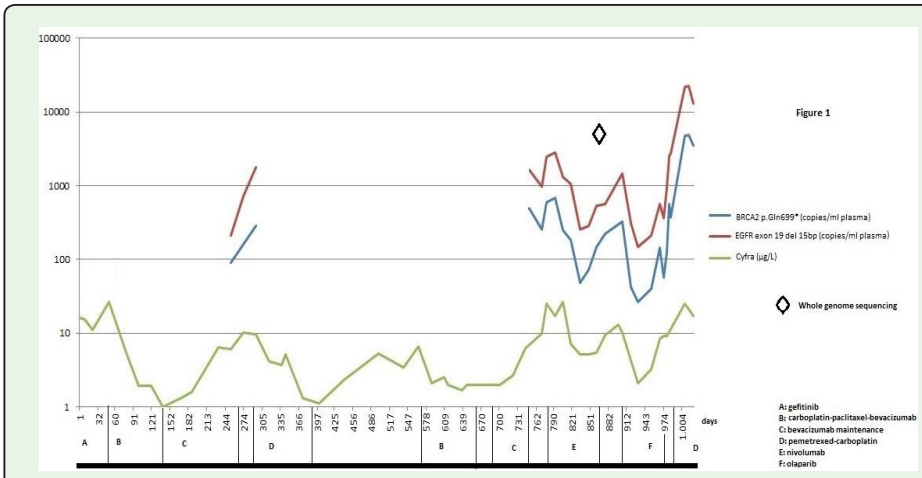

Figure 1: Shows plasma levels of Cyfra, frequency of Epidermal Growth Factor Receptor (EGFR) and breast cancer 2 (BRCA2) mutation in circulating tumor DNA. After start of olaparib (F) serum levels of BRCA2 and EGFR show a refractory decrease.

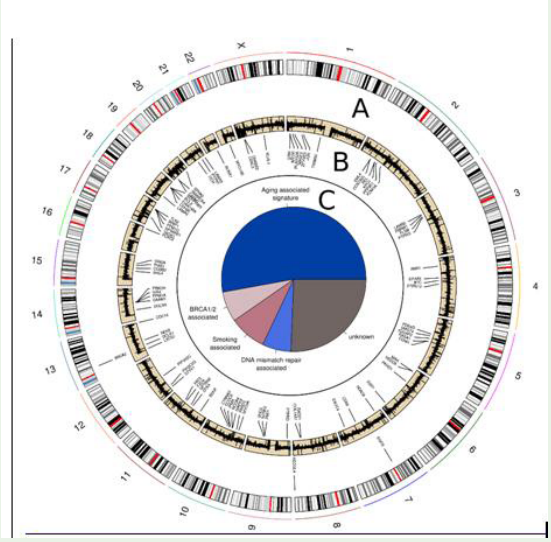

Figure 2: Shows mutations in Epidermal Growth Factor Receptor (EGFR) and breast cancer 2 (BRCA2) in the outer Circos (A), filtered with Clin Var. The middle circus (B) shows the copy number variations. The mutational signatures [4] are shown in (C), most dominant are aging, BRCA1/2, smoking, and DNA mismatch repair-associated transactions.

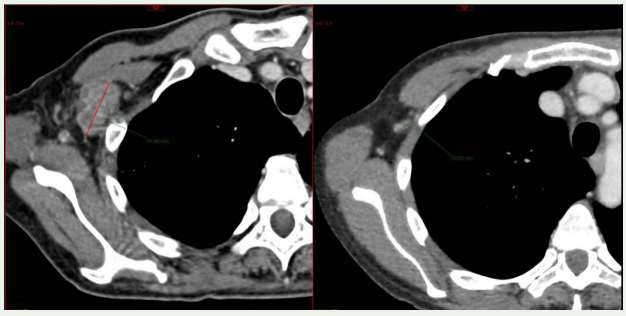

Figure 3: Shows axillary lymph node measuring 21 mm before treatment with olaparib (left picture) and measuring 8 mm after treatment with olaparib (right picture).

Discussion

EGFR mutations have been reported in up to 60% of selected Asian descendants with Non-Small Cell Lung Cancer (NSCLC) (female, never/light smoker, and adenocarcinoma) [1]. Prospective analysis showed that 70% of patients with EGFR mutations are responsive to TKIs. The EGFR protein is also involved in the repair of DNA Double Strand Breaks (DSB) [2].

BRCA2 is a tumor suppressor gene and is involved in DNA repair, replication and cell cycle control. Germline BRCA1/2 mutation-associated and BRCA-like tumors are rare in solid tumors but they tend to respond favorably to platinum based chemotherapy and other DNA-damaging agents [3].

Homologous Recombination Repair (HRR) is a pathway for error-free repair of DSB and for the recovery of stalled or collapsed DNA replication forks [2]. HRR-defective cells are hypersensitive to DNA lesions that block replication forks, such as DNA interstrand crosslinks produced by cisplatin [2]. Furthermore, impaired HRR is synthetically lethal with PARPi [2]. Mutated EGFR is closely linked to altered FAN1 (Fanconi Anemia-Associated Nuclease 1) and function and subnuclear localization downstream of FANCD2 (Fanconi anemia group D2), leading not only to platinum sensitivity but also sensitivity to PARPi [2]. We believe that this explains why our patient responded so well to carboplatin and olaparib.

The response to systemic treatment in NSCLC can be assessed at the blood level using the levels of Circulating Tumor DNA (ctDNA). Here we detected both BRCA2 and EGFR mutations in ctDNA in plasma using digital droplet polymerase chain reaction. Possibly, fluid phase response assessment will replace the classical radiological review, but now it should be used together with data from patient's condition and symptoms.

Patient Consent

The patient, described in this case report, gave permission for publication of her data.

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