CLINICAL VIGNETTE

Triple Negative Metastatic Breast Cancer and AKT1 Activation

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Patient Case

A 68-year-old female with triple negative (estrogen receptor and progesterone receptor negative, Her2 not overexpressed) metastatic breast cancer was originally diagnosed in 2022, Over the last 2 years her metastasis to lung and liver parenchyma have been controlled on sequential systemic therapy. Chemotherapy regimens have included carboplatin with paclitaxel, capecitabine and most recently on sacituzuamb govitecan. The last chemotherapy was given four months ago. On restaging, progressive disease was noted and next generation sequencing revealed an AKT1 E17K mutation.

This patient highlights an unexpected finding, presence of a AKT1 activating mutation in hormone negative breast cancer. In breast cancer patients, *AKT1* ^{E17K} mutation frequency ranges between 4 % and 8.2 %.[1] Pathogenesis of the *AKT1* ^{E17K} mutation had been thought to be restricted to estrogen receptor-positive ductal and lobular breast carcinomas. In these cancers, AKT is the key node of the phosphatidylinositol 3-kinase (PI3K)–AKT–PTEN signaling pathway leading to cell proliferation or apoptosis. Its activation leads to uncontrolled cell division. It was understood to be an estrogen receptor dependent pathway. Estrogen binding to the estrogen receptor in the cell nucleus activates AKT related proteins leading to increased and dysregulated cell division.[2]

Recent studies suggest that the AKT1 mutation may also be clinically relevant in ER negative breast malignancies. Estrogen can modulate cytoplasmic signaling in an estrogen receptor-independent manner. Eing-Mei et al. studied breast cancer cell lines without detectable estrogen receptors and demonstrated the proliferative effect of AKT1 can be directly stimulated by estrogen. The activation of Akt was evaluated using a phosphoserine antibody. They demonstrated direct Akt activation with estrogen, as indicated by phosphorylation at Ser473 of the oncoprotein, in ER-negative breast cancer cells. Activation of Akt by estrogen in these cells was time and dose dependent and could be blocked by inhibitors of phosphatidylinositol 3'-kinase and Src kinase but not by estrogen antagonists.[3]

A first in class AKT inhibitor, capivasertib, is now commercially available. In the CAPItello-291 registry phase III trial, capivasertib was studied in combination with Fulvestrant in relapsed hormone positive, HER2 not-overexpressed metastatic breast cancer. Capivasertib has not shown significant clinical activity as a single agent due to a variety of factors. These include redundant pathway signaling and receptor cross-talk and as such it was combined with fulvestrant. In the CAPITello-291 trial Faslodex with a placebo was compared to the capivasertib/ faslodex combination. The median progression-free survival was 7.2 months in the capivasertib–fulvestrant group, as compared with 3.6 months in the placebo–fulvestrant group (hazard ratio for progression or death, 0.60; 95% confidence interval [CI], 0.51 to 0.71; P<0.001). In the AKT pathway–altered population, the median progression-free survival was 7.3 months in the capivasertib–fulvestrant group, as compared with 3.1 months in the placebo–fulvestrant group (hazard ratio, 0.50; 95% CI, 0.38 to 0.65; P<0.001).[4]

These data are not as robust in hormone negative breast cancer. The PAKT trial reported some encouraging results. In this randomized double blinded phase II trial, capivasertib and paclitaxel was compared to placebo with paclitaxel as first-Line therapy for metastatic triple-negative breast cancer. Median PFS was 5.9 months with capivasertib plus paclitaxel and 4.2 months with placebo plus paclitaxel (hazard ratio [HR], 0.74; 95% CI, 0.50 to 1.08; 1-sided P = .06 [predefined significance level, 1-sided P = .10]). Median OS was 19.1 months with capivasertib plus paclitaxel and 12.6 months with placebo plus paclitaxel (HR, 0.61; 95% CI, 0.37 to 0.99; 2-sided P = .04). In patients with PIK3CA/AKT1/PTEN-altered tumors (n = 28), median PFS was 9.3 months with capivasertib plus paclitaxel and 3.7 months with placebo plus paclitaxel (HR, 0.30; 95% CI, 0.11 to 0.79; 2-sided P = .01). Based on these encouraging results further confirmatory studies are enrolling.[5]

For the patient described above there are no current commercially available regimens that directly target the AKT1 deleterious mutation. After review of available clinical trials and standard of care medications, she has opted to proceed on fam-trastuzamab-deruxtecan-nxki (Enhertu). Ideally in the future, AKT1 directed therapy will be available.

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