Dramatic response to cyclin D–dependent kinase 4/6 inhibitor in refractory poorly differentiated neuroendocrine carcinoma of the breast

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ABSTRACT

Neuroendocrine tumors are a rare subset of breast carcinomas. Commonly, platinum-based doublet is used as a systemic treatment option for high-grade neuroendocrine carcinomas from lung, gastrointestinal, and genitourinary origins. In comparison to other breast cancers, neuroendocrine carcinomas have unique genomic features and different treatment strategies. We present a patient with high-grade neuroendocrine carcinoma of the breast who had a successful and durable response to the cyclin D–dependent kinase (CDK) 4/6 inhibitor palbociclib in conjunction with endocrine therapy. This patient was refractory to commonly used platinum-based chemotherapy as well as hormone-based treatment. To date, this is the first published case of use of CDK 4/6 inhibitor in primary neuroendocrine carcinoma of the breast.

KEYWORDS Cyclin D–dependent kinase 4/6 inhibitor; neuroendocrine breast carcinoma; palbociclib

Neuroendocrine carcinoma of the breast is an aggressive tumor that has a higher local recurrence rate and inferior survival than invasive ductal carcinoma.^{1,2} Neuroendocrine breast cancers also present on average 10 years later and with a higher T stage than invasive ductal carcinomas.^{1,3} Poor prognostic factors for neuroendocrine breast carcinoma include advanced TNM stage, increased expression of Ki-67, the absence of progesterone expression, high nuclear grade, large tumor size, and regional lymph node metastasis.⁴ Neuroendocrine tumors of the breast commonly are estrogen receptor (100%) and progesterone receptor (50%) positive and human epidermal growth factor receptor 2 (Her2) negative, although Her2-positive cases have been reported.⁵ A few reviews have explored the different treatment options for primary neuroendocrine tumors of the breast. This case report examines the different types of systemic therapies that can be used to target neuroendocrine breast carcinomas.

CASE PRESENTATION

A 44-year-old Vietnamese woman presented to the emergency department for evaluation of sharp right upper-quadrant abdominal pain. She had no significant past medical, surgical, or family history. She had a 2- to 3-year

history of an unevaluated breast mass. Computed tomography of the chest and abdomen showed a 16-mm mass in the left breast, a left hepatic lobe lesion, and metastatic lesions in the thoracic and lumbar spine. Whole-body positron emission tomography (PET) scan was consistent with a fluorodeoxyglucose-avid breast mass as well as left axillary lymph nodes and osseous metastases, but no fluorodeoxyglucose-avid liver lesions were reported. Ultrasound-guided biopsy of the left breast mass demonstrated high-grade, estrogen receptor–positive, progesterone receptor–positive, Her2-negative breast cancer. Further histochemical analysis revealed a Ki-67 of 80% and positivity for CD56 and synaptophysin diagnostic of high-grade invasive neuroendocrine breast carcinoma (*Figure 1*).

The patient was started on carboplatin (area under the curve 5) and etoposide (100 mg/m² days 1–3) every 3 weeks. She was also started on zoledronic acid every 4 weeks for her bony metastases. A follow-up PET scan after two cycles of chemotherapy showed a slight reduction of hypermetabolic activity in the tumor in all sites but overall a modest response to therapy. After completing a total of six cycles of carboplatin and etoposide, a follow-up PET scan showed stable response in the breast and bony lesions but revealed two new hypermetabolic liver

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Figure 1. Synaptophysin staining of breast tumor. Highly positive staining of synaptophysin indicates that the tumor is neuroendocrine based.

lesions. Her chemotherapy was stopped and leuprolide and tamoxifen-based endocrine therapy was initiated. Liver magnetic resonance imaging after 1 month of Lupron and tamoxifen showed diffuse metastatic liver disease, so she was started on palbociclib 3 weeks on, 1 week off. After 1 month of follow-up, a new left supraclavicular lymph node was noted on physical exam, and her tamoxifen was changed to fulvestrant and a gonadotropin-releasing hormone agonist while palbociclib was continued.

The patient tolerated this regimen. Her PET scan after 3 months showed improvement in her breast malignancy as well as liver and skeletal metastases (*Figure 2*). After 18 months of improvement and progression-free survival, she was noted on imaging to have a new left hepatic lobe metastasis, but the remainder of her disease was stable. This new left hepatic lobe metastasis was biopsied for genomic sequencing while on palbociclib therapy. Genomic alterations by next-generation sequencing (Foundation

Figure 2. Magnetic resonance images before and after palbociclib therapy. (a, b) Pretreatment scans show diffuse liver and spinal metastases. (c, d) Scans after palbociclib treatment show improved liver and spinal metastases.

One) on the liver biopsy revealed *CCND1* amplification, *ESR1* Y537S mutation, *ARID1A* L1915fs*3 mutation, stable microsatellites, and an intermediate tumor burden (six mutations/Mb). She had no reportable alteration in the *ERBB2* gene. She subsequently received stereotactic radiotherapy to her liver lesion and has continued her palbociclib-based therapy.

DISCUSSION

There are no guidelines for management of neuroendocrine breast carcinomas. Our patient did not respond well to commonly used platinum doublet chemotherapies or tamoxifen and gonadotropin-releasing hormone agonist-based therapy. The best response was mounted to the combination of fulvestrant and palbociclib, with a progression-free survival of 18 months. This appears to be the first case in which palbociclib was used as a primary treatment with positive results for neuroendocrine breast cancer.

Chemotherapy targeted at high-grade neuroendocrine cancers is usually based on drug combinations commonly used for small cell carcinoma of the lung. A similar study that used this treatment plan and then followed up with tamoxifen did not achieve tumor regression, similar to our case.⁶ Another reported case of neuroendocrine carcinoma of the breast expressing estrogen receptor, progesterone receptor, and Her2 achieved remission using docetaxel, trastuzumab, and carboplatin.⁷ Because most neuroendocrine breast tumors are estrogen receptor and progesterone receptor positive, endocrine-based therapy may be an effective treatment strategy. Tamoxifen as sole therapy as well as adjuvant treatment after surgery has shown good outcomes.^{8,9}

In a case report, a neuroendocrine breast cancer that had metastasized to the liver had a promising response to peptide receptor radionuclide therapy.¹⁰ Gene families that could be potential targets include fibroblast growth factor receptor (*FGFR*), tyrosine kinase *KDR* (vascular endothelial growth factor receptor 2), and *HRAS*.¹¹ The *KDR* mutation is sensitive to vascular endothelial growth factor receptor kinase inhibitors, and research is ongoing into fibroblast growth factor receptor inhibitors.¹¹

Neuroendocrine breast carcinomas harbor an average of 4.5 somatic mutations, similar to luminal B carcinomas but fewer than luminal A carcinomas.¹² The genes that are most frequently associated with neuroendocrine carcinoma are *GATA3*, *FOXA1*, *TBX3*, and *ARID1A* as well as *PIK3CA*, *AKT1*, and *CDH1*.¹² Genomic analysis of the liver lesion noted on progression of palbociclib-based treatment revealed that she had *ESR1* Y537S and *ARID1A* L1915fs*3 mutations as well as *CCND1* amplification. Clinically, a *CCND1* amplification could predict enhanced sensitivity to cyclin D-dependent kinase (CDK) 4/6 inhibitors, such as palbociclib.¹³ CDK is important in tumor progression due to its function driving cell cycle proliferation, which is often unregulated and overexpressed in tumor cell lines.¹⁴ Cyclins, such as *CCND1*, regulate CDKs and specifically when bound to CDK4 and 6 will

function as a G1/S transition regulator in the cell cycle.¹⁵ This is in conjunction with what we found clinically, because she responded best to a combination therapy of palbociclib and fulvestrant. Palbociclib was determined to be the best treatment option because she had a modest response to cytotoxic chemotherapy usually directed at small cell carcinomas. Neuroendocrine carcinomas of the breast share a molecular profile similar to that of luminal A and B cancers and may behave like hormone-sensitive carcinomas, which is why the patient was treated with hormone-directed therapy. Further, results from the PALOMA 2 trial failed to demonstrate increased sensitivity to a combination of palbociclib and letrozole based on biomarker analysis of cell cycle-related genes.¹⁶

ESR1 mutations in breast cancer are related to metastasis, usually while on hormonal therapy.^{17,18} The *ARID1A* gene is a tumor suppressor gene, and an associated mutation or inactivation is reported in many cancers.¹⁹ Preclinical evidence shows that *ARID1A* inactivation may predict sensitivity to EZH2 inhibitors.²⁰ Other studies have shown that *ARID1A* inactivation may relate to the PI3K-AKT pathway activation and therefore may portend sensitivity to drugs that inhibit this pathway.²¹ Primary breast neuroendocrine tumors are rare, and limited literature-based therapeutic options are available. Our patient was refractory to chemotherapy and endocrine treatment but had a good response to the combination of palbociclib and endocrine therapy. Further research into CDK4/6 inhibitors in the treatment of neuroendocrine breast cancer is warranted.

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