Case Reports in Oncology

Case Rep Oncol 2019;12:494–499

DOI: 10.1159/000501304
Published online: June 26, 2019

Case Report

Somatic BRCA2 Mutation-Positive Concurrent Accessory Male Breast Cancer (BC) and Non-Small Cell Lung Cancer (NSCLC): Excellent Efficacy of Palbociclib, Fulvestrant and Leuprolide in Platinum-Exposed and Endocrine-Refractory BC Associated with Cyclin D1 and FGFR1 Amplification and of Carboplatin, Paclitaxel and Radiation in NSCLC

Yu Cheng[a] Ningjing Li[b] Ann Eapen[a] Ritesh Parajuli[a] Rita Mehta[a]

[a]Division of Hematology and Oncology, UC Irvine Medical Center, Irvine, CA, USA;
[b]Lutheran General Hospital, Park Ridge, IL, USA

Keywords
BRCA2 · Fulvestrant · Leuprolide · Male breast cancer · Palbociclib

Abstract
Accessory male breast cancer (BC) is a rare entity and is associated with poor outcome. We report a 76-year-old patient who was diagnosed with concurrent accessory breast and primary lung cancer, both were positive for somatic BRCA-2 (E1593D) mutation. He received concurrent radiation and platinum-based chemotherapy for lung cancer with good response, but breast cancer progressed in about 8 months, and further progressed after single agent anastrozole in 10 months. Next Generation Sequencing (NGS) of breast cancer was also positive for *CCND1* (Cyclin D1) and FGFR1 amplifications. Despite a poor molecular profile of breast cancer, and progression following platinum-based chemotherapy and anastrozole, he was successfully

Dr. Rita Mehta
101 The City Drive, Building 56, Rm. 236
Orange, CA 92868 (USA)
E-Mail rsmehta@uci.edu

treated with the Cyclin-dependent kinase (CKD) 4/6 inhibitor palbociclib, estrogen-receptor down-regulator fulvestrant and luteinizing hormone-releasing hormone (LHRH) agonist leuprolide with the duration of response of 21 months which has exceeded duration of response to prior treatments. This case is of interest given FDA expanded the approval of palbociclib in combination with AI or fulvestrant for male patients with HR–positive, HER2-negative metastatic breast cancer in Apr. 2019 based on real-world data from electronic health records.

Introduction

Accessory breast cancer is very rare, accounting for 0.3–0.6% of all breast cancers, it mostly presents as an axillary mass and can also grow in any part of the breast line (the line from axilla to groin) [1]. Males BC is almost exclusively hormone receptor positive, including the androgen receptor (AR), and is associated with a higher prevalence of *BRCA 2* germline mutations. The mainstay of systemic therapy for hormone receptor (HR)-positive male breast cancer is hormonal therapy. Tamoxifen is the most extensively studied. Other hormonal therapies include LHRH agonists, aromatase inhibitors (AIs), and fulvestrant have also been used in adjuvant and or metastatic settings. CDK inhibitors or mammalian target of rapamycin (mTOR) inhibitors used in combination therapy, as compared with endocrine therapy alone, have been reported to result in significantly improved outcomes in women with breast cancer [2–4]. Unfortunately, data on such treatment in male BC is lacking.

Case Report

We present the case of 76-year-old male with metastatic accessory breast cancer, who was successfully treated with combination of CKD4/6 inhibitor palbociclib, estrogen-receptor down-regulator fulvestrant and LHRH agonist leuprolide.

In January 2016, patient presented to the outside of hospital with a slowly growing right axillary mass over 3 years course. An excisional biopsy of the axillary mass was performed and invasive ductal carcinoma (IDC) of breast [estrogen receptor (ER)+, progesterone receptor (PR)+ and human epidermal growth factor receptor-2 (HER2)–] was diagnosed. A positron emission tomography/computed tomography (PET/CT) suggested uptake in right axillary and subcarinal lymph nodes, right parotid lesion, prostate, and two lung nodules in the right lower lobe measured 1 cm with SUV of 1.4 and 1.6. Subsequently the patient underwent right axillary tumor bed resection and sentinel lymph node (SLN) dissection. Final biopsy results of the mass showed IDC, grade 3, stage II pT2N0M0, ER+/PR+/HER–. Oncotype DX score was 27. And Foundation One NGS was positive for BRCA2 (E1593D) mutation as well as *CCND1* (Cyclin D1) and FGFR1 amplifications. Genetic test was negative for genetic mutation.

An endobronchial ultrasound (EBUS) and fine needle aspiration (FNA) of subcarinal lymph node were performed and showed poorly differentiated carcinoma. Immunohistochemistry (ICH) studies were consistent with primary lung adenocarcinoma with positive for TTF-1, NapsinA, and Keratin and negative for mammoglobin, ER, PR, and HER2. A core biopsy result of the right lung was suggestive of invasive adenocarcinoma. The patient was therefore diagnosed with stage IIIA NSCLC. Subsequently from Mar. to Apr. 2016, he underwent concurrent chemoradiation with three cycles of paclitaxel and carboplatin as well as a total 4,500 cGy radiation therapy in 25 fractions to the right lower lobe and subcarinal lymph node. In May

2016, PET/CT revealed a decrease in size of the hypermetabolic subcarinal lymph node. In June 2016, the patient underwent right lower lobe superior subsegmentectomy along with hilar and mediastinal lymph node dissection. Pathologic results suggested well differentiated to moderate differentiated adenocarcinoma, 1.6 cm with clean margins, no lymphovascular involvement, 0/7 lymph nodes involvement (ypT1aN0M0). IHC results consisted of negative EGFR, ALK, ROS1, and PDL1 22C3 INC 0%. Foundation One NGS was positive for BRCA2 (E1593D) mutation.

A complicated chylothorax, respiratory failure, and prolonged rehabilitation delayed starting anastrozole for breast cancer till Oct 2016, when a baseline PET/CT showed metastasis in right proximal femur. Patient subsequently transferred care to our institution, and PET/CT in August 2017 showed tumor progression. PET avid areas included right axillary lymph node, right proximal femur and right lower lobe pleural nodule (Fig. 1a). Subsequently an ultrasound-guided right axillary lymph node core biopsy and an FNA of right femur bone were performed. IHC results confirmed metastatic breast carcinoma with ER 100%, PR 95%, HER2 IHC/FISH negative and Ki 67 30–40%. Anastrozole was discontinued and patient was started on palbociclib, fulvestrant and leuprolide while continuing zometa. Patient has been tolerating the three-drug combination therapy relatively well except mild neutropenia, for which palbociclib had been decreased to 100 mg dosing. A series of CTs have showed very good response with the most recent PET/CT in February 2019 demonstrating complete resolution of right axillary lymph node, resolution of pleural nodules and minimally sclerotic lesion in the right femur (Fig. 1b).

Discussion and Review of Literature

To our knowledge, this is the first case report showing a clinically meaningful response to a combination of CKD 4/6 inhibitor, fulvestrant and LHRH agonist in metastatic male breast cancer.

Most data regarding treatment of male breast cancer is retrospective and comes from small single-institution series, thus the choice of treatment modalities is generally guided by extrapolation of data from female breast cancer. Since male BC is almost always ER+, the preferred treatment option for 1st line therapy of metastatic disease is endocrine therapy. Tamoxifen is the treatment of choice, and upon relapse, other therapeutic options should be considered like aromatase inhibitors preferably used with LHRH agonist or fulvestrant [5]. The combinations of endocrine and molecular agents like CDK4/6 inhibitors have been approved in metastatic BC, but data specific to male breast cancer is lacking. BRCA2 mutation associated cancers display DNA-repair deficiency and are particularly susceptible to DNA-repair inhibition and DNA-damage with PARP inhibitors and platinum, respectively.

Our patient had a near complete response to concurrent platinum-based chemoradiation therapy in the setting of BRCA2-mutation-positive lung cancer after resection, but demonstrated eventual disease progression of BRCA 2-mutation-positive breast cancer. He had stable disease on anastrozole for about 10 months, similar to a case series of men treated with aromatase inhibitor with or without LHRH agonists [6]. The eventual resistance was likely driven by activation of feedback loop of higher FSH and LH and testicular steroidogenesis induced by lower estrogen caused by anastrozole as well as due to escape signaling, likely driven by Cyclin D1 and FGFR1 in this patient.

Fulvestrant, a selective estrogen-receptor down-regulator, binds competitively to ERs in breast cancer cells, leading to ER deformation and decreased binding of estrogen [7]. In

metastatic breast cancer, fulvestrant in combination with palbociclib, a CDK4/6 inhibitor was associated with significant PFS benefit and a trend toward overall survival compared to fulvestrant alone in patients whose disease had progressed after cytotoxic chemotherapy and or aromatase inhibitor [8]. Furthermore, LHRH agonists are known to desensitize the pituitary hormone (LH) and follicle-stimulating hormone (FSH) with resultant fall in ovarian estrogens. Indeed, in premenopausal women in PALOMA-3, LHRH agonist was added to block ovarian steroidogenesis. However, this study did not include male breast cancer patients. Given the feasibility and efficacy of adding LHRH agonist in premenopausal women in PALOMA-3, we used the LHRH agonist in our male patient to block testicular steroidogenesis.

Interestingly, our patient had somatic BRCA2 E1593D mutation both in lung and breast cancer. The durable response of poorly differentiated lung cancer to carboplatin and paclitaxel and radiation was likely due to additive/synergistic effect of DNA damage inducing effect of concurrent platinum and radiation-based therapy. Moreover, use of both platinum-based therapy and PARP inhibitors has been associated with PFS benefit in metastatic BC with germline BRCA mutation [9–11]. We show that in a patient who had received prior platinum, the combination of fulvestrant and palbociclib remains efficacious even in the setting of somatic BRCA2 mutation. This may have further relevance in treatment of somatic and germline BRCA-mutation positive patients, given efficacy of PARP inhibitors in BRCA-germ-line mutation positive breast cancer and for germ-line and somatic mutation ovarian cancer. Moreover, our patient had both Cyclin D1 *(CCND1)* and FGFR1 amplifications in breast cancer. Both Cyclin D1 and FGFR1 amplifications have been shown to predict poor clinical outcome in ER-positive breast cancers and are associated with the emergence of endocrine resistance. The combination of CKD4/6 inhibitor with AI or fulvestrant has shown consistent benefit in setting of Cyclin D1 amplification while FGFR1 amplification has been reported to induce resistance to CDK4/6 inhibitor combination therapies both in cell lines [12] and clinical study [13]. Interestingly, our patient achieved a durable remission despite presence of FGFR mutation, suggesting that the combination of fulvestrant, palbociclib and leuprolide may delay emergence of resistance. In future, upon progression, FGFR inhibitors may offer precision guided treatment option [14].

Conclusion

In this paper, we have described a very rare case of a male metastatic breast carcinoma arising in an accessary mammary gland. Our case shows the combination of CKD 4/6 inhibitor, fulvestrant and LHRH agonist has a clinically meaningful benefit in the setting of acquired endocrine-refractory and platinum-pretreated metastatic male breast cancer with somatic BRCA2 mutation, FGFR1 and Cyclin D1 amplification. Our patient was treated before the recent FDA expanded approval of palbociclib in combination with AI or fulvestrant for male patients with HR–positive, HER2-negative metastatic breast cancer based on real-world data from electronic health records. Judicious use of medications in men based on their approval in female breast cancer is warranted given the rarity of male breast cancer. Our patient also had a good response to platinum-based chemotherapy and concomitant radiation in somatic BRCA2-positive lung cancer. And due to the rarity of male breast cancer, studies of breast cancer treatment should enroll both females and males to build an evidence base that supports future treatment recommendations.

Statement of Ethics

The patient provided written informed consent to publish this case.

Disclosure Statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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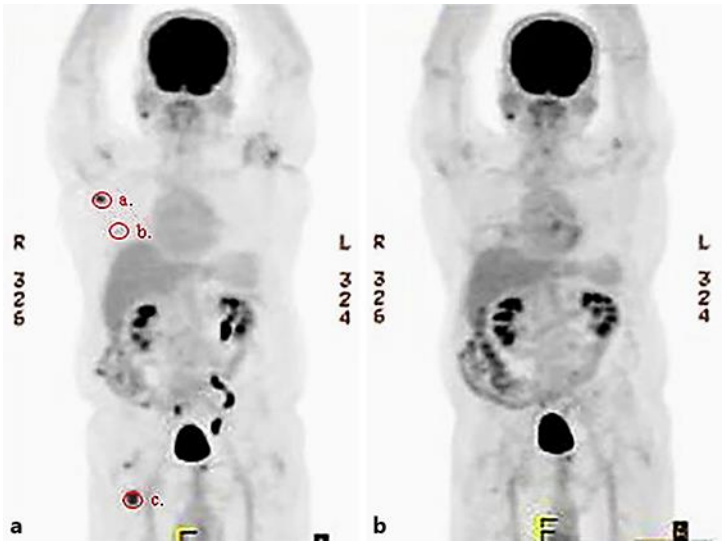

Fig. 1. Target lesions on PET/CT before therapy (**a**) and after 18 months therapy (**b**). a., right axillary lymph node; b., right lower lobe pleural nodule; c., right proximal femur lesion.