Male patient with metastatic stage IV breast cancer achieves complete remission on second line Abemaciclib, Fulvestrant and Leuprolide: A case report

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Abstract. Male breast cancer occurs rarely, comprising <1% of breast cancers. Due to the low incidence of male breast cancer, clinical trials of this disease are lacking. Therefore, therapeutic strategies utilized in the management of female breast cancer are often applied to male patients with breast cancer. Specifically, clinical outcomes using CDK 4/6 inhibitors require further investigation in male patients. To the best of our knowledge, the present report presents the first known case of a male patient treated with second line Abemaciclib, Lupron and Fulvestrant, producing complete remission. To the best of our knowledge this is also the first report of complete remission in a male breast cancer patient with a regimen utilizing a CDK 4/6 inhibitor.

Introduction

Male breast cancer is a rare entity that shares many overlapping features with female breast cancer (1). Although female breast cancer has been extensively studied, far less is known about male breast cancer. As with women, the incidence of breast cancer in men increases with age and males are typically diagnosed 5 to 10 years later than females (2-8). Furthermore, the incidence of male breast cancer seems to be increasing (9). Family history of breast cancer appears to play an important role in the development of male breast cancer (10). For example, men with a family history of breast cancer in a female or male relative have two to three times the risk of developing breast cancer themselves (11-13). BRCA2 mutations are well described as causal factors for male breast cancer. Multiple studies have demonstrated that 4-15% of men with breast cancer carry deleterious BRCA2 mutations (14-16). BRCA1 mutations are less commonly seen with <5% of male breast cancer patients harboring the mutation (14,16-18). Other genes have also been implicated in male breast cancer risk including mutations in PTEN tumor suppressor gene (Cowden syndrome), TP53 (Li-Fraumeni syndrome), PALB2, and mismatch repair genes (Lynch syndrome) (19-21). Other risk factors for male breast cancer include androgen/estrogen imbalance and environmental exposures (10). Histologically, 85-90% of males present with invasive ductal carcinomas (22,23). Since males lack acini and lobules in the normal male breast lobular carcinoma is rare in male breast cancer (9,24). Other histologic variants are rare but have been observed (25). Over 80% of male breast cancer is hormone positive with some series showing estrogen (ER) positivity as high as 99% (10,23). Rates of human epidermal growth factor receptor (HER2) overexpression in male breast cancer have been variable in different studies ranging from 2 to 45% (26-30). Cardoso *et al* (23) conducted immunohistochemistry evaluations of male breast cancer patients and found 42% luminal A-like, 42% luminal B-like, 8.7% HER2 positive, and 0.3% triple negative expression amog male breast cancer patients.

Prospective randomized trials in the treatment of male breast cancer are lacking due to the rarity of this entity. Furthermore, little data exists on the activity of CDK 4/6 inhibitors in the treatment of hormone positive metastatic breast cancer in male patients. In this report we describe the first known case of a male patient treated with second line Abemaciclib, Lupron, and Fulvestrant producing a dramatic and durable complete remission. This is the first known case of a male achieving complete remission on a CDK 4/6 inhibitor.

Case report

We present a case of a 39 year old male with no past medical history who initially palpated a mass in his left breast in March 2015. A diagnostic mammogram and left breast ultrasound showed an irregular mass measuring 9x7x7 mm in the outer left breast at 3 o'clock suspicious for malignancy. In March 2015 he underwent left mastectomy with pathology demonstrating grade II infiltrating ductal carcinoma, 1.6 cm

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tumor with extensive lymphovascular invasion, five of five lymph nodes positively involved, and margins negative. The invasive component was estrogen receptor 58% positive, progesterone receptor 7% positive, human epidermal growth factor receptor 1+ not overexpressed/negative (Fig. 1). Of note, a computed tomography scan (CT) of the chest abdomen pelvis and a bone scan were performed and negative for metastatic disease. The patient was staged as pT1cN2aMx stage IIIA. He was treated with adjuvant chemotherapy with Adriamycin and Cyclophosphamide followed by Paclitaxel then radiation therapy to the chest wall and regional lymphatics (left supraclavicular fossa 5,000 cGy, left chest wall 5,000 cGy, left scar boost 1,000 cGy) ending December 2015. In December 2015 the patient was started on Tamoxifen 20 mg orally daily and was doing well until a restaging MRI in April 2017 identified a solitary metastatic lesion to the sternum. No biopsy was performed at this time. He received palliative radiation (4,000 cGy) to the sternal lesion which was completed in June 2017. A follow-up CT chest abdomen and pelvis October 2017 showed numerous bilateral pulmonary nodules suspicious for metastatic disease. His local team switched him to Anastrazole in June 2017. Patient presented for initial consultation to our facility October 2017 where a biopsy to confirm metastatic disease and to obtain genomic information was requested. Patient underwent video assisted thoracoscopy and wedge resection of two pulmonary nodules in left upper and lower lobes November 2017. Pathology was consistent with metastatic adenocarcinoma compatible with breast primary (Fig. 2). Genomic testing on the lung biopsy specimen revealed PIK3CA amplification, GATA 3 mutation, stable microsatellites, and a low tumor mutational burden. Genetic testing revealed absence of deleterious mutations for the BRCA1 or BRCA2 genes. In November 2017 a baseline 18F-fluorodeoxyglucose-positron emission tomography computed tomography (FDG-PET CT) was performed post wedge resection showing metastatic disease to subcarinal lymph node, left hilum, and osseous metastatic disease involving the 5th cervical vertebral body, 2nd lumbar vertebral body, the ninth right rib (Fig. 3). Baseline labs: CA 15-3 was 45.2 U/ml (0.0-35.0 U/ml), CA 27.29 was 60 U/ml (<38 U/ml), complete blood count with white blood cell (wbc) count 5.2 K/μl, hemoglobin 17.2 g/dl, platelet count 134 K/μl (150-450 K/μl), absolute neutrophil 2.15 K/μl, complete metabolic panel was normal except for elevated aspartate aminotransferase (AST) 69 U/l (17-59 U/l), alanine aminotransferase 135 U/l (21-72 U/l), and testosterone level 1,240 ng/dl (132-813.0 ng/dl).

The patient was initiated on Abemaciclib 150 mg orally twice daily, Fulvestrant 500 mg intramuscular injection days 1, 15, 29 then monthly there after, and Leuprolide 7.5 mg intramuscular injections every month in November 2017. Additionally, he was given Denosumab 120 mg subcutaneously every month for prevention of skeletal related events. The patient tolerated treatment well with grade 1 fatigue, grade 1 hot flashes, grade 3 diarrhea mitigated by Loperamide and resolved. Testosterone levels appropriately suppressed <50 ng/dl. Patient also had transient grade 2 thrombocytopenia which resolved spontaneously and persistent grade 2 neutropenia. Follow-up PET CT February 2018 showed resolution of the hypermetabolic osseous metastatic foci with sclerosis at prior locations also there was resolution of the previously described abnormal metabolic activity in the left hilar and subcarinal mediastinal regions. Patient's subsequent PET CT imaging every 3 months remained negative with last PET CT June 2019. Patients tumor markers normalized in December 2017 with episodic mild flare up in CA 27.29. Last tumor markers over past 10 months remained negative June 2019. Patient is clinically asymptomatic and developed a grade 3 neutropenia in October 2018 requiring dose reduction of Abemaciclib to 100 mg po BID. So far the patient remains in a durable complete remission for 18 months on this treatment regimen.

Discussion

Due to the rarity of male breast cancer, treatment approaches used for female breast cancer patients in the metastatic setting are often applied to males with metastatic breast cancer. Given that most males with metastatic breast cancer are hormone positive, hormonal therapy is often the first approach in the absence of visceral crisis (31). Tamoxifen is considered standard of care frontline therapy for males with metastatic disease (32,33). Luteinizing hormones-releasing hormone agonists with or without anti-androgens have been shown to be effective in male breast cancer (34-36). Aromatase inhibitors have shown clinical activity in male breast cancer with increased clinical benefit observed with the addition of a GnRH analogue (37). Data regarding the role of Fulvestrant are limited. One pooled analysis of 23 male patients receiving Fulvestrant in the first, second, or third line setting reported a partial response rate of 26% and an additional 48% had stable disease (38). Resistance to hormonal therapy in the metastatic setting is common and most patients will eventually experience progression of disease (39). Research into the mechanisms of resistance to endocrine therapy had shed light on cell cycle regulation, particularly the cyclin-dependent kinases (CDKs). The CDKs play an important role in regulating cell-cycle progression (40).

The cyclin-dependent kinases, CDK4 and CDK6, are responsible for regulating the cell cycle by initiating the transition of cells through the G1 restriction point (41). A common feature in human cancers is the dysregulation and aberrant activation of CDK4 and 6 therefore promoting cell cycle progression (42,43). Inhibition of CDK4 and CDK6 seems like a rational therapeutic target to prevent the progression of tumor cells through the G1 restriction point. Various preclinical studies have been conducted and support CDK4 and CDK6 as potential tumor targets (22,44-46). Subsequently three CDK4/6 inhibitors have been approved for use in patients with metastatic breast cancer in the first or second line setting: Palbociclib (PD-0332991; Pfizer), Ribociclib (LEE011; Novartis), and Abemaciclib (LY2835219; Lilly). Palbociclib was the first FDA approved CDK 4/6 inhibitor in combination with Letrozole as initial therapy for postmenopausal women with advanced hormone positive, HER2 negative metastatic breast cancer based on the results from the phase II PALOMA-I clinical trial (47). In PALOMA-I, patients who received Palbociclib and Letrozole experienced a roughly doubling of the progression free survival compared to treatment with Letrozole alone (47). These results were later confirmed in the randomized phase III study PALOMA-II (48). In the second line

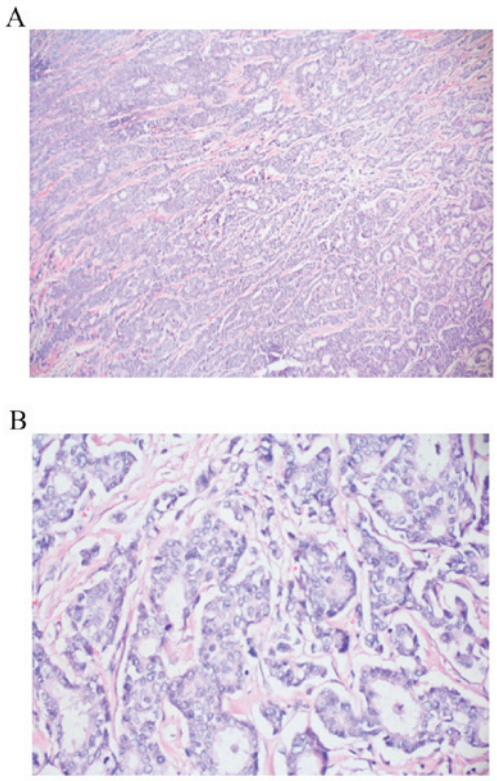

Figure 1. Invasive ductal carcinoma. (A) A combination of tubules and solid ribbons are observed under a 4X objective (final magnification, x40). (B) Under a 20X objective, nuclear pleomorphism is demonstrated, with one case of mitosis (final magnification, x200). The overall grade was determined to be 2/3.

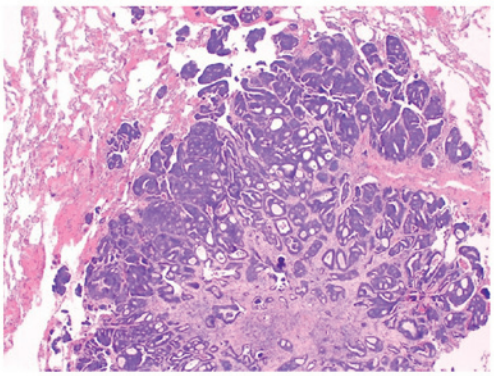

Figure 2. Invasive ductal carcinoma obtained via lung wedge resection conducted in 2017. The tumor fills 4/5 of the photographed field and exhibits tumor replacing lung tissue, with central fibrosis surrounded by nests and tumor glands. Lung parenchyma is observed in the upper left and upper right corner (final magnification, x100).

setting, Palbociclib was paired with Fulvestrant vs. Fulvestrant alone in patients with metastatic hormone positive HER2 negative breast cancer who had progressed on prior endocrine therapy in the PALOMA III randomized phase III trial (49). The study also included pre and perimenopausal females who were required to take Goserelin (49). The combination of Palbociclib and Fulvestrant produced a significant 9.2 month progression free survival compared with 3.8 in the Fulvestrant and placebo arm (49). Abemaciclib is an inhibitor of CDK4 and CDK6 and in enzymatic assays is 14 times more potent against CDK4/cyclin D1 than CDK6/cyclin D3 (50).

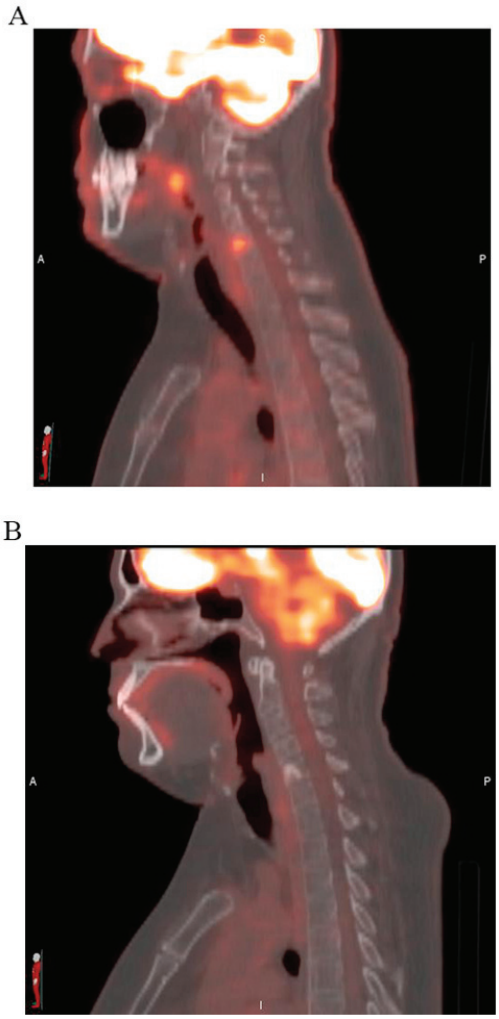

Figure 3. Baseline PET CT scans. (A) Sagittal view demonstrating metastatic disease to the 5th vertebral body of the cervical spine. (B) Post treatment PET CT demonstrating resolution of FDG activity involving the 5th vertebral body of the cervical spine with overlying sclerosis.

Fujiwara *et al* (51) conducted a phase 1 study of single-agent Abemaciclib in Japanese patients with advanced metastatic solid tumors where 5/12 (41.6%) patients were males. They concluded that single agent Abemaciclib demonstrated anti-tumor activity as a single agent and had an acceptable safety profile (51). In another phase I study, Abemaciclib as a single agent demonstrated antitumor activity in patients with several cancers with an ORR of 26% in patients with hormone refractory hormone positive metastatic breast cancer (52). Based on the single agent activity observed with Abemaciclib, the phase II MONARCH 1 study was launched (53). In this open label phase II single arm trial, women with hormone positive HER2 negative metastatic breast cancer who had progressed on or after prior endocrine therapy and had 1 or 2 prior chemotherapy regimens in the metastatic setting were enrolled (53). In this study patients who received single agent administered on a continuous schedule had an overall response rate of 19.7% with a median progression free survival of 6 months (53). Based on the results of MONARCH-I, the U.S. Food and Drug Administration approved Abemaciclib to be used alone to treat women and men diagnosed with hormone positive HER2 negative metastatic breast cancer that

has progressed after hormone therapy and prior chemotherapy in the metastatic setting. Abemaciclib was also studied in the randomized phase III trial MONARCH 2, where Abemaciclib and Fulvestrant vs. Abemaciclib and placebo were studied in patients with hormone positive HER2 negative metastatic breast cancer who had progressed on prior endocrine therapy (54). The combination of Abemaciclib and Fulvestrant yielded a significantly improved PFS of 16.4 months compared with 9.3 months in the Fulvestrant and Placebo arm (54). Data regarding treatment responses to CDK 4/6 inhibitors in males is extremely limited. The first reported response in males was demonstrated in 2016 by S. Sorcher where a male with metastatic breast cancer achieved a partial response to Palbocliclib and Letrozole in the fifth line setting (55). The second known report by Castrellon *et al* (56) demonstrated a case of a male with metastatic breast cancer to lung and bone who achieved partial response to CDK 4/6 therapy with Palbociclib and Fulvestrant. Here we report the first male patient with metastatic breast cancer to achieve complete remission on a CDK 4/6 inhibitor. Given the lack of randomized controlled trials in male breast cancer treatment decisions are often extrapolated from data derived from female breast cancer trials. The standard of care for females with metastatic hormone positive HER2 negative metastatic breast cancer who progress on endocrine therapy is treatment with CDK 4/6 inhibitor with Fulvestrant. Our patient was treated as per MONARCH-II protocol given the significant benefit of the addition of Abemaciclib to Fulvestrant compared with Fulvestrant alone (54). Furthermore, Abemaciclib is the only CDK 4/6 inhibitor with an FDA approval in males and it has been previously studied in male cancer patients (51,52). It should be noted however among the three FDA approved CDK 4/6 inhibitors (Abemaciclib, Palbociclib, Ribociclib) no head to head trials have been performed therefore no superior agent has been identified in cancer patients. The relative favorable side effect profile and response seen in this patient utilizing the combination of Fulvestrant, Abemaciclib and Lupron seems encouraging and further reports of CDK4/6 drug combinations may show responses. Identification of predictive biomarkers of response to CDK inhibitors represents one of the most important clinical areas of interest as CDK inhibitors have become the accepted first line treatment in metastatic hormone receptor positive HER2 negative breast cancer. Despite the excellent clinical advancement afforded by CDK inhibition a significant percent (20%) of patients will not respond to CDK inhibition. Therefore identification of predictive biomarkers of response to CDK inhibition is prudent. Studies are slowly emerging in this field. Gong *et al* (57) analyzed the sensitivity of 560 cell lines to the selective CDK4/6 inhibitor abemaciclib and they found that cell lines with genomic features of D-cyclin activating features are particularly sensitive. Clinically however no reproducible predictive biomarker has emerged. For example in a phase II study using Palbociclib as a single agent in advanced breast cancer assessed progression free survival and Rb expression, KI-67, p16 loss, and CCND1 amplification. In this study there was no association between these biomarkers and response to therapy (58). Several studies are ongoing to elucidate potential predictive biomarkers. If more clinicopathologic and predicitive biomarker data could be accumulated on CDK 4/6 drug combinations in males with metastatic hormone positive male breast cancer this would help facilitate clinicians in selecting optimal therapeutic algorithms for individual males with breast cancer.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

DH provided clinical management for the patient and developed their treatment protocol. DH also conceived the present study, wrote the manuscript, reviewed the treatment of stage IV male breast cancer and CDK 4/6 inhibitors for use in breast cancer, and supervised the study. SJ clinically treated the patient, and partially wrote and revised the manuscript. JS assembled pathological images and partially wrote the manuscript. RV assembled radiographic images and partially wrote the manuscript. RA wrote, critically revised and approved the manuscript, and developed the treatment protocol. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present case report was reviewed and approved by the Ethics Committee of the Cancer Treatment Centers of America.

Patient consent for publication

The patient verbalized consent for the publication of their information in a medical journal, which was documented in the medical record of the patient.

Competing interests

The authors declare that they have no competing interests.

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