HHS Public Access

Author manuscript

Clin Breast Cancer. Author manuscript; available in PMC 2019 June 01.

Published in final edited form as:

Clin Breast Cancer. 2018 June ; 18(3): e277–e280. doi:10.1016/j.clbc.2017.12.008.

Complete Response to Single Agent Palbociclib in Metastatic Breast Cancer: A Case Report

Sri Lakshmi Hyndavi Yeruva[1], **Mehrbod Som Javadi**[2], and **Vered Stearns**[2,*]

[1]Howard University

[2]Johns Hopkins University School of Medicine

Introduction

Breast cancer is the most common malignancy diagnosed in women and it is the second leading cause of cancer-related death in United States.[1] Estrogen and Progesterone receptor (ER/PR)-positive, human epidermal growth factor receptor 2 (HER2)-negative is the most common subtype of breast cancer.[2] While most patients in Western societies present with early stage breast cancer and will likely survive their disease, some patients suffer a recurrence, and other present with *de novo* metastatic disease. Once metastatic, breast cancer is rarely cured, with a 5-year survival rate of only 24%.[1]

Endocrine manipulations are an integral part of treatment of patients with advanced ER/PR-positive breast cancer.[3] Unfortunately, patients with metastatic disease will eventually suffer disease progression despite endocrine therapy either due to primary or secondary resistance. Depending on initial response, most women will be transitioned to chemotherapy following 1–3 lines of endocrine therapy.[4] In contrast to endocrine therapy, chemotherapy is associated with many adverse effects, and once initiated women are expected to have more frequent office visits and laboratory tests. Therefore, there has been a search to improve efficacy of endocrine therapy, to delay the administration of chemotherapy, and to maintain the quality of life of these patients.

Palbociclib, is an orally active, selective, and reversible inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Palbociclib is approved by the Food and Drug Administration (FDA) for the treatment of postmenopausal women with hormone receptor-positive, HER2-negative disease in combination with endocrine therapy.[5] It is approved in combination with aromatase inhibitors as an initial treatment based on the results of PALOMA-1 and PALOMA-2 studies.[6,7] Palbociclib is also approved with fulvestrant in women with disease

*Correspondence to: Vered Stearns, MD, Professor of Oncology, Breast Cancer Research Chair in Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, 1650 Orleans Street, CRB1-Room 144, Baltimore, MD 21287-0013, Phone: 443-287-6489, Fax: 410-614-4073, vstearn1@jhmi.edu.

Conflict of Interest

VS received research grant support from Novartis and Pfizer.

progression following first line endocrine therapy based on PALOMA-3.[8,9] We report here a case of a post-menopausal woman with metastatic breast cancer who had substantial clinical benefit with single agent palbociclib as second line therapy.

Case report

A 73-year-old woman presented for treatment recommendations for recurrent metastatic breast cancer in 2010. She was initially diagnosed with ductal carcinoma *in-situ* in 2000, following an abnormal mammogram. Her past medical history was significant for hypertension, hyperthyroidism, and a hysterectomy and unilateral salpingo-oophorectomy at age 28. Her home medications were hydrochlorothiazide and levothyroxine, and a prolonged use of oral hormone replacement therapy. Her family history was significant for ovarian cancer in her mother and maternal aunt and prostate and colon cancer in her father. Given the family history of ovarian cancer and her desire to continue hormone replacement therapy, she underwent bilateral mastectomy with breast reconstruction and an oophorectomy. Pathology of the left breast revealed a high grade, 1 cm ductal carcinoma *in-situ*. She declined genetic testing and received no further therapy.

In 2010, the patient underwent an assessment in preparation for an extensive reconstructive foot surgery, which required bone marrow harvesting and stem cell engraftment. A PET-CT revealed a single hypermetabolic mass of 2.3 x1.8 cm in the right lobe of her liver. A biopsy revealed this was a poorly differentiated adenocarcinoma, consistent with a breast primary. It was ER/PR-positive, HER2-negative. She stopped her hormone replacement therapy when the diagnosis of metastatic disease was made. Her physical examination was unremarkable except for prior bilateral mastectomies and implant-based reconstruction. The patient was started on endocrine therapy with exemestane. She described multiple symptoms and was not able to tolerate the medication. She was prescribed anastrozole, which was associated with a syncopal episode.

Since the patient had an oligo-metastasis, she underwent a partial hepatectomy in April 2010, which revealed metastatic adenocarcinoma carcinoma. Following the hepatic resection, she declined endocrine therapy. She was followed regularly with clinical examination and PET-CT imaging every 3 to 6 months. After 3 years of follow up, PET-CT revealed a new single hypodense lesion in the liver measuring 2.6 × 2.8 cm. The patient underwent a second hepatic resection in June 2013.

The patient again declined endocrine therapy and was with no evidence of disease until June 2014 when multiple new hepatic lesions were seen on PET-CT. Since she was not a candidate for resection, the patient started letrozole and has taken the medication despite significant bone pain and dry mouth for approximately one year when a PET-CT in June 2015 demonstrated disease progression with multiple hepatic nodules and mediastinal lymph nodes (Figure 1). The patient was started on fulvestrant and palbociclib in July 2015. She received one injection of fulvestrant and described significant flu-like symptoms, including a cough and diffuse aches. She declined day 15 dose, and did not take her palbociclib. She was agreeable to a second dose of fulvestrant about one month following the first injection and also started palbociclib. She again described significant side effects and declined endocrine

therapy. She also declined chemotherapy and asked to remain on single agent palbociclib. Given few available options, the patient was maintained on palbociclib, which was adjusted to 100 mg by mouth daily for 2 weeks with a 2-week break based on her complete blood cell counts. She tolerated this dose and schedule well with no neutropenia. An initial follow up PET-CT in September 2015 revealed near complete metabolic resolution of the metastatic disease (Figure 2). She remained on palbociclib alone and was monitored with clinical evaluation and PET-CTs every 3 to 6 months. However, after progression free interval of 20 months her PET CT, in June of 2017 revealed disease progression in the liver and locoregional lymph nodes.

Discussion

CDKs are key regulators of cell cycle and RNA transcription. Inhibition of CDK prevent phosphorylation of retinoblastoma protein (Rb) downstream and arrests cell cycle in G1 phase *in vitro* and tumor regression *in vivo*.[10,11] Animal studies have demonstrated that oral administration of palbociclib as a single agent is associated with inhibition of cell growth and suppression of DNA replication by preventing cell from entering S phase. Oral administration of palbociclib is also associated with significant tumor regression against multiple human tumor xenografts in mice.[12]

In a phase II trial of single agent palbociclib, investigators enrolled 37 women with metastatic breast cancer with positive staining for Rb (>1+ staining intensity in primary or metastatic tumor). The majority of the patients (84%) had hormone receptor-positive, HER2-negative disease and received 2 or more prior cytotoxic regimens (76%) and endocrine therapies (65%). Overall, the investigators reported a clinical benefit rate of 21% in patients with hormone receptor-positive disease, which increased to 29% among those who had progressed through at least 2 prior lines of endocrine therapy. This study suggested that palbociclib may have single agent activity, primarily in women with acquired endocrine resistance. However, the median progression-free survival (PFS) in hormone receptor-positive, HER2-negative disease was only 3.8 months (95% confidence interval [CI] 1.9 – 5.8).[13]

Our patient received only one line of endocrine therapy prior to initiating palbociclib. Her PFS on letrozole was similar to that observed in the control arms of PALOMA-1 and 2. PALOMA-1, a randomized, open label, phase 2 multicenter trial, and PALOMA-2, a phase 3, randomized double-blind study, enrolled postmenopausal women with advanced hormone-receptor positive, HER2-negative breast cancer who have not received prior therapies to letrozole with palbociclib or placebo. In PALOMA-1, the median PFS was 10.2 months in the letrozole group and 20.2 months for the palbociclib and letrozole group (HR 0.488, 95% CI 0.319–0.748; p=0.0004).[6] In PALOMA-2, the median PFS was 14.5 months (95% CI, 12.9 to 17.1) in the placebo-letrozole, as compared with 24.8 months (95% CI 22.1 to not estimable) in the palbociclib and letrozole group (HR for disease progression or death, 0.58; 95% CI, 0.46 to 0.72; P<0.001).[7]

Our patient had prolonged response to palbociclib alone, longer than the benefit she experienced with letrozole alone, and longer than the median PFS seen in PALOMA-3 with

the combination of palbociclib and fulvestrant and in the single agent palbociclib trial. In the phase 3 randomized PALOMA-3, women aged 18 years or older with hormone receptor positive, HER2-negative metastatic breast cancer received fulvestrant with or without palbociclib.[8] A median PFS of 9.5 months (95% CI 9.2–11.0) was observed in the fulvestrant and palbociclib group compared to 4.6 months (95% CI 3.5–5.6) in the fulvestrant and placebo group (HR 0.46, 95% CI 0.36–0.59, p<0.0001). These 3 studies demonstrated significant improvement in PFS when palbociclib was added to endocrine therapy, however, our patient was not taking concomitant endocrine therapy.

Two additional CDK inhibitors have been recently approved for individuals with advanced breast cancer. Ribociclib, was approved in combination of AI for first line therpay of women with advanced hormone receptor-positive, HER2-negative breast cancer. Single agent ribociclib administered to heavily pretreated patients with solid tumors or lymphomas was associated with modest activity including one partial response in a patient with a PIK3CAmutant, CCND1-amplified, ER-positive breast cancer, and several stable diseases in patients with breast cancer.[14] Abemaciclib was approved for second or later-line therapy in combination with fulvestrant based on the results of MONARCH-2, and as a single agent for third or later-line therapy for women and men based on MONARCH-1.[15,16]

Another observation is that our patient had a family history of ovarian cancer but has declined genetic testing. It is possible that individuals with germline mutations may be particularly sensitive to CDK 4/6 inhibition. Future mechanistic studies can help further investigate this hypothesis.

Our case report suggests that single agent palbociclib may provide benefit to select patients. Future studies should consider patient populations who may be candidates for this approach, which may help delay administration of chemotherapy while providing good disease control. Further large multicenter trials are needed to see the effect of single agent palbociclib on disease progression.

Conclusion

This is the first report to our knowledge of a patient treated with single agent palbociclib for metastatic breast cancer in clinical practice. Further studies are needed to assess response to single agent palbociclib instead of combination with endocrine therapy in patients who either cannot tolerate endocrine therapy or had disease progression on endocrine therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported in part by NIH grant P30 CA006973 (VS).

References

1. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016; 66:271–89. [PubMed: 27253694]
2. Nadji M, Gomez-Fernandez C, Ganjei-Azar P, Morales AR. Immunohistochemistry of estrogen and progesterone receptors reconsidered: experience with 5,993 breast cancers. Am J Clin Pathol. 2005; 123:21–7. [PubMed: 15762276]
3. Rugo HS, Rumble RB, Burstein HJ. Endocrine Therapy for Hormone Receptor Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline Summary. J Oncol Pract. 2016; 12:583–7.
4. Briest S, Stearns V. Chemotherapeutic Strategies for advanced breast cancer. Oncology (Williston Park). 2007; 21:1325–35. discussion 38, 40. [PubMed: 18080617]
5. Beaver JA, Amiri-Kordestani L, Charlab R, et al. FDA Approval: Palbociclib for the Treatment of Postmenopausal Patients with Estrogen Receptor-Positive, HER2-Negative Metastatic Breast Cancer. Clin Cancer Res. 2015; 21:4760–6. [PubMed: 26324739]
6. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015; 16:25–35. [PubMed: 25524798]
7. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016; 375:1925–36. [PubMed: 27959613]
8. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016; 17:425–39. [PubMed: 26947331]
9. Walker AJ, Wedam S, Amiri-Kordestani L, et al. FDA Approval of Palbociclib in Combination with Fulvestrant for the Treatment of Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer. Clin Cancer Res. 2016; 22:4968–72. [PubMed: 27407089]
10. Finn RS, Dering J, Conklin D, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res. 2009; 11:R77. [PubMed: 19874578]
11. Shapiro GI. Cyclin-dependent kinase pathways as targets for cancer treatment. J Clin Oncol. 2006; 24:1770–83. [PubMed: 16603719]
12. Fry DW, Harvey PJ, Keller PR, et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Mol Cancer Ther. 2004; 3:1427–38. [PubMed: 15542782]
13. DeMichele A, Clark AS, Tan KS, et al. CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. Clin Cancer Res. 2015; 21:995–1001. [PubMed: 25501126]
14. Infante JR, Cassier PA, Gerecitano JF, et al. A Phase I Study of the Cyclin-Dependent Kinase 4/6 Inhibitor Ribociclib (LEE011) in Patients with Advanced Solid Tumors and Lymphomas. Clin Cancer Res. 2016; 22:5696–705. [PubMed: 27542767]
15. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2-Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol. 2017; 35:2875–84. [PubMed: 28580882]
16. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(−) Metastatic Breast Cancer. Clin Cancer Res. 2017; 23:5218–24. [PubMed: 28533223]

Clinical practice points

- Palbociclib combined with endocrine therapy is currently approved for the treatment of metastatic hormone receptor-positive breast cancer.
- The effect of single agent palbociclib is not well known, however a benefit may be observed in patients who cannot tolerate endocrine therapy.

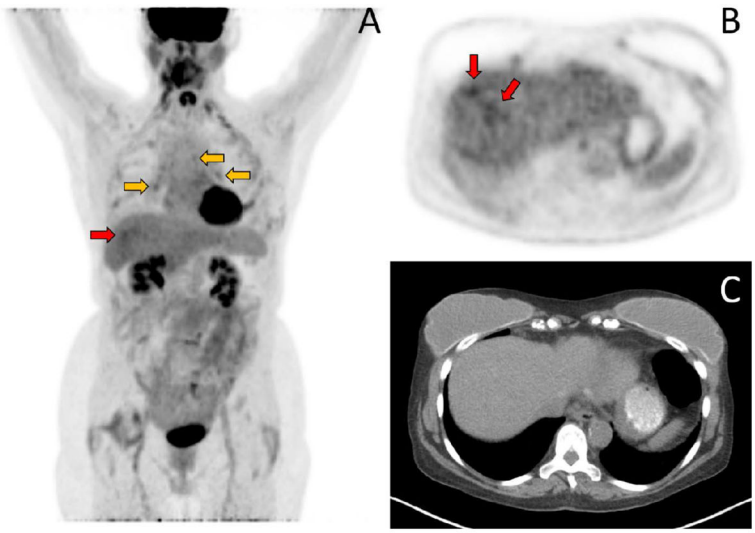

Figure 1. PET-CT images prior to initiating palbociclib

Maximum Intensity Projection PET image (A) demonstrate multiple focally hypermetabolic lymph nodes in the mediastinum/hilum (yellow arrows) and patchy nodular activity in segment 7 of the liver (red arrow). Axial PET-CT images (B and C) demonstrate patchy nodular hypermetabolic disease in liver segment 7 (red arrows).

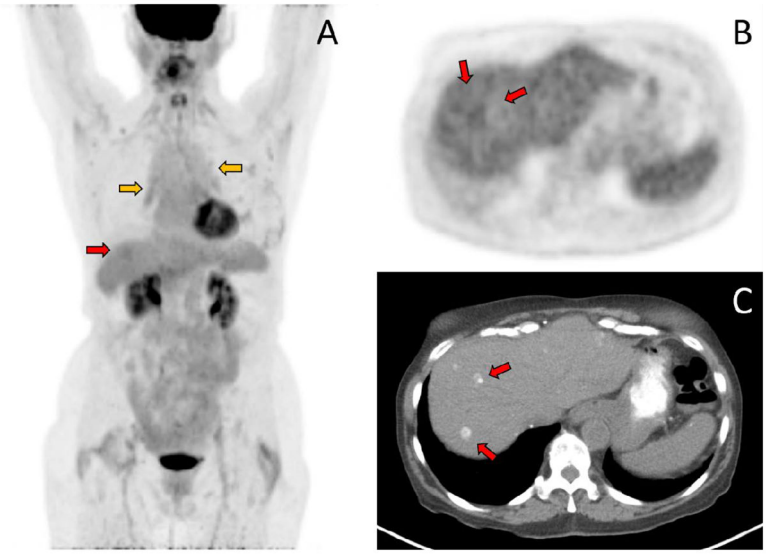

Figure 2. PET-CT images following 3 months of single-agent palbociclib

Maximum Intensity Projection PET image (A) demonstrates near complete metabolic resolution of lymph nodes in the mediastinum/hilum (yellow arrows) and lesions in segment 7 of the liver (red arrow). Axial PET-CT images (B and C) demonstrates metabolic resolution of multiple liver lesions in segment 7 with post treatment calcification (red arrows).