Palbociclib added to ongoing endocrine therapy for hormone receptor-positive HER2-negative metastatic breast cancer: A case report series

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Received September 11, 2019; Accepted February 3, 2020

DOI: 10.3892/mco.2020.2016

Abstract. Palbociclib is a potent cyclin-dependent kinase (CDK)4/6 inhibitor that disrupts cell cycle progression and has been recently approved in combination with an aromatase inhibitor or fulvestrant as first- and second-line treatment in hormone receptor (HR)$^+$, human epidermal growth factor receptor (HER)2$^-$ metastatic breast cancer. There is evidence that palbociclib may reverse endocrine therapy resistance and that it may also be added to ongoing endocrine therapy beyond progression to obtain clinical benefit. The aim of the present study was to explore this possibility in 5 patients who received palbociclib + fulvestrant following disease progression while under treatment with fulvestrant alone. The median progression-free survival was not reached during a median follow-up of 25 months, and the most frequent best response was stable disease. Three patients remained under treatment on the last re-evaluation. All patients had highly endocrine-sensitive disease and had previously received fulvestrant for ≥12 months. The hypothesis that a selected subpopulation of patients with HR$^+$/HER2$^-$ metastatic breast cancer may benefit from the addition of palbociclib to ongoing endocrine therapy beyond disease progression merits further investigation.

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Key words: endocrine therapy, endocrine resistance, endocrine sensitization, breast cancer, palbociclib, fulvestrant, case report

Introduction

Palbociclib is a selective, potent and orally available inhibitor of cyclin-dependent kinase (CDK)4/6 that exerts antitumor effects by disrupting cell cycle progression from the G1 to the S phase (1). The combination of palbociclib and tamoxifen synergistically reduced tumor growth in preclinical studies conducted in hormone receptor (HR)$^+$ breast cancer (BC) cell lines and xenografts (2). Recent clinical trials confirmed the important antitumor activity of palbociclib when combined with different types of endocrine therapy (ET) in women with HR$^+$ metastatic BC (MBC) (3-5). Importantly, data from the PALOMA-3 study, which specifically enrolled women with MBC whose disease progressed while on ET, or within 12 months following completion of adjuvant therapy, indicate relevant clinical activity in the setting of patients truly resistant to ET (5). This is in line with pre-clinical evidence indicating that adding palbociclib to ET may partially reverse endocrine resistance, particularly that acquired through previous treatments (6).

Current clinical guidelines include palbociclib combined with an aromatase inhibitor (AI) or fulvestrant as standard first- or second-line treatment for HR$^+$/human epidermal growth factor receptor (HER)2$^-$ MBC patients with *de novo* or relapsing disease following administration of an AI as adjuvant or first-line therapy (7,8). However, the optimal sequence of therapies in HR$^+$/HER2$^-$ MBC has yet to be clearly established, and CDK4/6 inhibitors cannot be added to an endocrine agent already being administered for metastatic disease. In fact, to the best of our knowledge, none of the pivotal trials conducted to date has tested the efficacy of palbociclib in reversing resistance to previous ET. In our Institution (University of Naples Federico II) when palbociclib was approved but not yet commercially available, it was administered in combination with fulvestrant in a cohort of patients who had progressed

while on first-, second- or third-line treatment with fulvestrant alone and a previous AI. We herein report our anecdotal clinical experience with this agent.

Case reports

We retrospectively report the clinical history of 5 postmenopausal patients affected by $HR^+/HER2^-$ MBC who were previously treated with fulvestrant as first- or second-line therapy, who received palbociclib + fulvestrant as second- or third-line therapy after disease progression while on previous ET. All patients had already received an AI in the metastatic and/or early setting. When palbociclib was added to ET, none of the 5 patients had a visceral crisis, which is a condition defined as severe organ dysfunction based on signs and symptoms, laboratory studies, and rapid progression of the disease (8). Response to treatment was assessed every 3-4 months while the patients were on palbociclib according to RECIST 1.1 (9). Palbociclib was made available by Pfizer®, who provided the drug before it was made publicly available in Italy. All patients were adequately informed before agreeing to the treatment, which was administered at the University of Naples Federico II Hospital. Written informed consent was obtained from all patients to participate in the study and for the publication of this case report. Any potentially identifying information was omitted. Ethics Committee approval for retrospective studies, such as the present, is not mandatory under Italian law. The median progression-free survival (PFS) of our series with 95% confidence interval (CI) was estimated according to Brookmeyer and Crowley (10) using R software for Mac OS X, version 3.5.0 (package survival) (11).

The best obtained response, treatment duration, major adverse drug reactions (ADRs), and metastatic sites upon palbociclib initiation are summarized in Table I.

Case 1. The first patient was a 56-year-old woman without relevant comorbidities, first diagnosed in July 2015 with invasive ductal carcinoma (IDC) of the right breast, pT3 pN1, intermediate-grade (G2), estrogen receptor $(ER)^-$ and progesterone receptor $(PR)^+$ (~90% expression for both), Ki67 proliferative index 30% and $HER2^-$. The patient was initially treated with right radical mastectomy and ipsilateral axillary lymphadenectomy. Preoperative staging was negative for metastatic disease. Since the patient had a persistent cough that started a few months before the BC diagnosis, a whole-body computed tomography (CT) scan was performed, which revealed several liver and lung nodules. A biopsy of one of the liver lesions revealed $HR^+/HER2^-$ IDC, which was consistent with the primary tumor. Weekly paclitaxel at 80 mg/m^2 was started as first-line therapy for MBC in September 2015. In January 2016 paclitaxel was discontinued due to a central venous access infection and grade 3 peripheral neuropathy. Letrozole was then started as maintenance ET at the standard dose of 2.5 mg/day *per os*. Tumor progression was detected after ~10 months of AI (October 2016); thus, letrozole was discontinued and fulvestrant 500 mg i.m. was administered every 4 weeks after an initial 2-week induction (henceforth defined as fulvestrant SD). In February 2017, due to progression of the liver disease, palbociclib was added to fulvestrant at a dose of 125 mg daily for 21 consecutive days followed by 7 days off therapy for a cycle of 28 days (standard schedule). Overall, the treatment was well-tolerated, except for persistent G3 neutropenia after the third cycle of therapy, after which time the palbociclib dose was decreased from 125 to 100 mg daily. In February 2018, after recovery from a G4 non-febrile neutropenia, palbociclib was further reduced to 75 mg. The disease remained stable according to RECIST throughout the whole treatment, until disease progression. In May 2018, due to the increase of the lung and liver lesions, palbociclib and fulvestrant were suspended and chemotherapy was started. The patient is still undergoing treatment.

Case 2. A 75-year-old woman, also suffering from hypertension and cataract, was initially diagnosed with early BC in 1992. At the time of initial diagnosis, the patient was 50 years old and was treated with right breast quadrantectomy and ipsilateral axillary lymph node dissection for a pT2 pN0 ER^+ and PR^+ with unknown HER2 status invasive lobular carcinoma (ILC). The patient also received standard adjuvant radiotherapy after surgery and adjuvant tamoxifen at the standard dose of 20 mg daily *per os*. In March 2010, a right breast nodule was surgically resected. The pathology report described the lesion as a G2, ER^+ and PR^+ (90 and 80% expression, respectively), Ki67 50% and $HER2^+$ (immunohistochemical score 3+) ILC. As no other lesions were present on a postoperative CT scan, the patient was put on trastuzumab for 18 months, in combination with letrozole at the standard dose of 2.5 mg daily *per os*. Letrozole was continued until July 2012, when a new nodule was identified on the surgical scar on clinical examination. At that point, a right radical mastectomy was performed, and analyses of the resected breast tissue revealed a G2, ER^+ and PR^+ (40 and 50% expression, respectively), Ki67 30% and $HER2^-$ ILC. After surgery, adjuvant treatment with weekly paclitaxel at 80 mg/m^2 was administered for 12 weeks, and oral exemestane at the standard dose of 25 mg daily *per os* was initiated. After 12 months of treatment, a new skin lesion appeared on the right chest wall. A tumor biopsy was performed and a new ER^+ and PR^+, Ki67 30% $HER2^-$ ILC lesion was diagnosed. As the skin lesion was not resectable, it was treated by radiotherapy, and systemic treatment with fulvestrant SD was prescribed in November 2013. The patient remained on fulvestrant for ~4 years. In June 2017, clinical examination and positron emission tomography (PET)/CT scans revealed new lesions on the right chest wall and in lymph nodes from the left axilla and right retroclavicular areas. A biopsy of the chest wall skin lesions revealed an $HR^+/HER2^-$ ILC. At this point, palbociclib was added to fulvestrant. The treatment was well-tolerated, the main ADRs being G1 neutropenia and anemia, and a low, occasional and intermittent increase in creatinine and urea. No dose reduction was deemed necessary. The best response obtained with the combination treatment was a partial response. The treatment is currently ongoing.

Case 3. A 71-year-old woman without relevant comorbidities was diagnosed with left BC in July 2004. The patient underwent left breast quadrantectomy and ipsilateral axillary lymphadenectomy for a pT1c pN0 IDC, G2, ER^+ and PR^+ (90% expression for both), Ki67 15% and $HER2^-$. At that time, the patient was treated with adjuvant radiotherapy on the residual breast and anastrozole at the standard dose of

Table I. Summary of treatment performance and initial disease burden per patient.

Patients	Metastatic sites prior to PALBO introduction	Disease-free interval	Duration of FULV before PALBO (months)	Duration of FULV + PALBO (months)	Best tumor response	Current status	Main ADRs
1	Lung and liver nodules, several lymph nodes and bone lesions	MAB	5	15	SD	PD	G2 leukopenia, G4 neutropenia
2	Skin nodule on the right chest wall, left axillary and right retroclavicular lymph nodes	18 years	43	28	PR	Ongoing treatment	G1 neutropenia, G1 anemia, G1 hypercreatininemia, G1 increased urea
3	Right lung inferior, superior and middle lobe and multiple lesions in the left lung superior lobe	10 years	24	25	PR	Ongoing treatment	G3 neutropenia, G1 leukopenia
4	Right parietal bone, right humeral head, sternal extremity of the left clavicle, posterior arch of the III and VIII ribs, bodies of several thoracic and lumbar vertebrae, left iliac wing, pubic symphysis, right acetabulum and ischium	MAB	7	13	SD	PD	G4 neutropenia, G3 leukopenia, G2 anemia, G2 trombocitopenia
5	Retroperitoneal lombo-aortic and left abdomino-pelvic mesenterial lymph nodes and bone lesions on the right iliac wing	2 years	12	18	SD	Ongoing treatment (FULV alone)	G2 leukopenia and G3 neutropenia

MAB, metastatic *ab initio*; ADRs, adverse drug reactions; SD, stable disease; PR, partial response; PD, progressive disease; PALBO, palbociclib; FULV, fulvestrant; G, toxicity grade.

1 mg daily. Ten years later, in September 2014, due to pain and paresthesia in the right arm, the patient underwent a spine magnetic resonance imaging examination that revealed metastatic lesions in the 7th cervical vertebra (C7) and in the 1st dorsal vertebra (D1). A biopsy was performed on C7 and the histological report confirmed the diagnosis of metastatic ER^+ (20% expression), PR^- and $HER2^-$ BC. Radiotherapy was performed on the bone metastases as palliative therapy for the pain, and first-line ET with fulvestrant SD was initiated soon thereafter. In September 2015, denosumab 120 mg s.c. every 4 weeks was added to the therapy. Two years later, in September 2017, a routine follow-up whole-body CT scan revealed multiple bilateral lung lesions. The PET scan results were consistent with the diagnosis of pulmonary metastases, and palbociclib in standard schedule was added to fulvestrant. After 6 months of therapy, the lung lesions had completely disappeared on the CT scan and the previously irradiated bone metastases had not increased in size. No major toxicity was observed, apart from G3 neutropenia, between June and July 2019, which led to a palbociclib dose reduction to 100 mg. G1 leukopenia was the only other adverse drug reaction recorded. The treatment was still ongoing at the last follow-up in October 2019.

Case 4. A solid, painless, left breast central mass measuring 9x7 cm, associated with nipple retraction, was identified in an 82-year-old woman in October 2013. Biopsy of the breast mass revealed an ER^+ and PR^+ (90 and 80% expression, respectively), G2, Ki67 30% and $HER2^-$ IDC. Bone and total body CT scans revealed multiple bone metastases to the right parietal bone, right humeral head, sternal extremity of the left clavicle, posterior arch of the III and VIII ribs, the bodies of several thoracic and lumbar vertebrae (the largest lesions being at L5 and T10), the left iliac wing, pubic symphysis, right acetabulum and ischium. Therefore, the patient was started on first-line therapy with letrozole 2.5 mg and zoledronic acid 4 mg every 4 weeks i.v. In September 2015, zoledronic acid was suspended after almost 2 years, and 1 year later it was replaced by denosumab. In February 2017, while still on letrozole, due to a notable increase in the size of the breast lesion, fulvestrant SD was initiated. In September 2017, due to bone disease progression, palbociclib was added to fulvestrant and denosumab. After the first cycle, palbociclib was interrupted on day 14 and then reduced from 125 to 100 mg due to G4 neutropenia. Due to persistent G3 neutropenia, the palbociclib dose was further reduced to 75 mg in March 2018. Other reported toxicities included G3 leukopenia, G2 anemia and G2 thrombocytopenia. The best response obtained was stabilization of the disease at the breast and bone sites, until October 2018, when bone and liver disease progression led to treatment discontinuation and chemotherapy with 80 mg/m^2 paclitaxel every 3 weeks out of 4 and bevacizumab every 2 weeks i.v. was prescribed. The patient is currently under treatment.

Case 5. An 82-year-old woman was diagnosed with BC in June 2014. The patient underwent left mastectomy and ipsilateral axillary lymphadenectomy for a pT2 pN3 ER^+ and PR^+ (90 and 20% expression, respectively) G2, Ki67 12%, $HER2^-$ ILC. Comorbidities included acute myocardial infarction with subsequent implantation of a pacemaker, and osteoporosis. Due to these comorbidities, the patient received only weekly paclitaxel at 80 mg/m^2, without anthracyclines as adjuvant chemotherapy, followed by adjuvant radiotherapy to the right chest wall and ipsilateral axilla. Adjuvant letrozole 2.5 mg was started in December 2014. Two years after the onset of adjuvant ET, in September 2016, a reassessment performed with PET/CT scan revealed tumor progression in multiple retroperitoneal lombo-aortic, abdomino-pelvic and mesenterial lymph nodes, as well as a new bone lesion in the right iliac wing. Due to the disease progression, letrozole was discontinued and replaced by fulvestrantdose In October 2017, palbociclib at a standard dose was added to treatment due to nodal progression of the disease. Stable disease was the best response achieved, and was confirmed by further reassessments. G2 leukopenia and G3 neutropenia were the only toxicities reported. Prolonged G3 neutropenia that required several dose adjustments led to palbociclib discontinuation in April 2019. The patient is currently on treatment with fulvestrant.

Discussion

In the present case series, palbociclib was prescribed in combination with fulvestrant following progression on fulvestrant alone in patients who had also previously received an AI. The median follow-up was 25 months [95% CI: 25 months - not assessable (NA)]. Interestingly, all 5 patients responded to the combination treatment: 3 patients achieved stable disease and 2 had a partial response, and all achieved at least 9 months of non-progressive disease. In fact, the median duration of palbociclib and fulvestrant therapy in our series was not reached (95% CI: 14.9 months-NA). In the pivotal PALOMA-3 trial, upon disease progression on AI monotherapy, patients switched to an alternative ET agent, fulvestrant, plus palbociclib. The median PFS of patients in the experimental arm was 9.5 months (95% CI: 9.2-11.0) (5). It is currently unknown whether extending the same ET beyond disease progression and adding palbociclib, instead of switching to palbociclib + an alternative endocrine agent, may be effective, particularly in patients who benefited from the previous ET. Recently, the TREND study explored whether reversal of resistance by adding CDK4/6 inhibition to the same ET continued beyond progression may be clinically useful (6). In this trial, patients progressing to first- or second-line ET with either an AI or fulvestrant who were started on a subsequent line of ET with palbociclib in combination with the same endocrine agent, had a median PFS of 10.8 months (6). Notably, the biggest advantage in terms of PFS was observed in patients who had received a prior line of ET for at least 6 months (6). This was concordant with data from the PALOMA-3 study showing that patients with sensitivity to previous ET gained a substantial benefit by receiving a combination of palbociclib and fulvestrant, in contrast with those characterized by intrinsic resistance to ET (5). In our series, all patients had highly endocrine-sensitive disease, with a long disease-free interval from previous surgery (3 patients with non-metastatic disease at diagnosis), ranging from 2 to 18 years, and a duration of fulvestrant prior to palbociclib addition ranging from 5 to 43 months. This may explain the very long duration of the combined treatment of palbociclib and fulvestrant, and further

supports the hypothesis that tumor endocrine sensitivity may be a good predictive marker of outcome for the combination of palbociclib and fulvestrant. Interestingly, taken together, the TREND results and the data of the present study also suggest that, in carefully selected patients previously treated with ET, palbociclib may play a role in reversing endocrine resistance to the same endocrine agent. There were several important limitations to the present study: this was a very small case series, most patients had oligometastatic and not visceral disease, and responded well to previous hormonal therapy; therefore, the findings of the present study may not be applicable to all patients with $HR^+/HER2^-$ MBC. However, data from our series and the TREND trial collectively suggest that adding a CDK4/6 inhibitor to ET beyond disease progression may be a viable therapeutic strategy, particularly in a selected patient population with a satisfactory outcome from the prior line of ET. However, this hypothesis requires further investigation and should be addressed in prospective and possibly randomized clinical trials.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

FS, IDS, CGR, MV, GB, CDA, CC, RL, MG, VF, GT, PM, GL, AA, LM, SDP and GA were directly involved in patient care. All authors have directly contributed to the study conception and design. FS, IDS and CGR retrieved data from patients' charts. IDS, FS and GA wrote the first draft of the manuscript. All authors contributed to the manuscript revisions, have read and approved the final version.

Ethics approval and consent to participate

All patients provided written informed consent to participate in the study. Ethics Committee approval for retrospective studies, such as this case series, is not mandatory under Italian law.

Patient consent to publication

Written informed consent was obtained from all patients regarding the publication of the case details and any associated images. Any potentially identifying information was omitted.

Competing interests

GA, MG and SDP declare honoraria from Roche, Pfizer, Astra-Zeneca, Novartis, Celgene, Lilly and Eisai. LM is a consultant for Pfizer, Astra-Zeneca, Novartis and a grant recipient of Pfizer. All other authors declare that they have no competing interests.

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