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Do CDK 4/6 Inhibitors, in Combination with Anti-Estrogen Therapy, Improve Morbidity and Mortality in Women with Advanced Breast Cancer Compared to Anti-Estrogen Therapy Alone?

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Do CDK 4/6 Inhibitors, in Combination with Anti-Estrogen Therapy, Improve Morbidity and Mortality in Women with Advanced Breast Cancer Compared to Anti-Estrogen Therapy Alone?

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not CDK 4/6 inhibitors, in combination with anti-estrogen therapy, improve morbidity and mortality for women with advanced breast cancer compared to anti-estrogen monotherapy.

Study Design: Systematic review of three randomized-controlled trials. All three articles were published in English between 2015 and 2016.

Data Sources: Two randomized, double-blinded, placebo-controlled trials and one open-label randomized controlled trial found using PubMed and NCBI.

Outcomes Measured: Each study assessed morbidity and mortality based on progression-free survival or overall clinical benefit (stable disease, partial response, or complete response by 24 weeks).

Results: All three studies showed significant prolongation of progression-free survival in patients that received treatment with anti-estrogen therapy plus an oral CDK 4/6 inhibitor for their estrogen receptor-positive, HER2neu negative metastatic breast cancer compared to anti-estrogen therapy alone or with placebo. Cristofanilli et al. found that median progression-free survival improved from 4.6 months to 9.5 months with combination therapy. Similar results were seen in Finn et al. with median progression-free survival of 20.2 months in those receiving combination therapy, compared to 10.2 months in women treated with anti-estrogen therapy alone. In the study by Hortobagyi et al., the progression-free survival rate at 18 months for those treated with CDK4/6 inhibitor was 63%, compared to 42.2% in the placebo group.

Conclusions: These studies suggest that cyclin dependent kinase 4/6 inhibitors used in conjunction with anti-estrogen therapy should be considered as an efficacious treatment regimen for postmenopausal patients with hormone receptor-positive, HER2neu negative advanced breast cancer. Finn and Hortobagyi, and colleagues, investigated the use of an aromatase inhibitor, letrozole, for anti-estrogen therapy. Cristofanilli and colleagues studied the efficacy of an estrogen receptor downregulator, fulvestrant. Additionally, palbociclib was used for inhibition of the CDK4/6 pathway in two studies, while ribociclib was used in the other. Improvement in progression-free survival and overall response was seen in all three studies regardless of the combination of drugs being used.

Key Words: Cyclic dependent kinase, palbociclib, fulvestrant, advanced breast cancer

INTRODUCTION

Breast cancer is characterized by the formation and growth of malignant cells within breast tissue. It is the most commonly diagnosed cancer in women, and the second leading cause of cancer death in this group.[1] Approximately 3.5 million women in the US are living with breast cancer; it is estimated that another 252,710 new cases will be diagnosed in 2017.[1] In 2010, the estimated cost of treating breast cancer in the US was ~$16.5 billion, and that number is expected to increase to $20.5 billion by 2020.[2]

Breast cancer can be classified as in situ (confined to its site of origin) or invasive disease, and has multiple molecular subtypes. Age is the most common risk factor for breast cancer, with the majority of diagnoses made after age 50. Additional risk factors include genetic tendency, positive family history of breast or ovarian cancer, having dense breasts or prior benign breast disease, sedentary lifestyle, diet high in saturated fat, excess alcohol consumption, and the use of HRT.[1] Additionally, due to extended exposure to hormones, women who have early menarche or late menopause are at an increased risk for developing breast cancer.

Mammography has become a useful tool in detecting breast cancer. The American Cancer Society recommends that women ages 40 to 44 have the *choice* to start yearly screening mammograms, and those women 45 and older should be screened annually.[3] At age 55, annual screenings can continue, or a woman can choose to have the exam performed every two years instead.[3] It is recommended that screening start sooner for high-risk individuals (e.g. strong family history, known genetic mutation). Breast cancer can be asymptomatic, with the first sign of disease being an abnormality seen on imaging studies. Those with symptomatic disease might notice a palpable breast mass, change in breast contour or the overlying skin, or nipple discharge. Additionally, patients with malignancy may complain of fatigue. Symptoms of advanced breast

cancer are commonly associated with disease location; breast cancer most commonly metastasizes to regional lymph nodes, bones, lung, liver and brain. An individual may subsequently experience lymphadenopathy, bone/back pain, nausea and vomiting, anorexia, weight loss, dry cough, shortness of breath, or changes in mentation.

Treatment of breast cancer is a multi-factorial approach and can include breast surgery with lumpectomy or mastectomy, axillary biopsy and resection, radiation to local or metastatic disease, systemic chemotherapy, and endocrine therapy. Patients with bony disease might also benefit from bisphosphonate derivatives. When considering clinical treatment, three genetic distinctions are considered: 1) estrogen receptor status 2) progesterone receptor status, and 3) HER2neu gene overexpression.[4] Of those diagnosed with invasive disease, ~71% are hormone receptor-positive, HER2neu negative.[1] Roughly 5% of women have stage 4 disease at the time of diagnosis, and the estimated 5-year survival for those with distant metastatic disease is 26%.[5] For these patients, hormonally directed therapy remains the mainstay of treatment, but is seldom effective as these patients can quickly develop endocrine resistance.[4,6,7] Managing these resistant cases continues to be a challenge within the medical community. Alteration in the cell cycle is a well-known characteristic in the development and spread of cancer. Multiple studies have investigated the role of various signaling pathways and receptor mutations that contribute to such cases. Cyclin dependent kinases (CDK) are a group of kinases that work together with regulatory proteins to control progression through the cell cycle; alteration and activation of the CDK 4/6 axis has been found to be a common feature in hormone receptor-positive cancer.[4] Studies have found that inhibiting this pathway is associated with arresting sensitive human breast cancer cells in the G1 phase of their cell cycles, with the effect being especially potent in receptor-positive breast cancers.[4] This paper evaluates three randomized controlled trials comparing the efficacy

of combination therapy with cyclin dependent kinase 4/6 inhibitors and anti-estrogen medications at improving progression-free survival in patients with advanced disease.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not CDK 4/6 inhibitors, in combination with anti-estrogen therapy, improve morbidity and mortality for women with advanced breast cancer compared to anti-estrogen monotherapy.

METHODS

The author of this selective review searched articles using PubMed and NCBI. Key words in the search included cyclin dependent kinase, palbociclib, fulvestrant, and advanced breast cancer. Articles were considered if they were relevant to the clinical question and included POEMs, were written in English, and had been published within the last 10 years. Exclusion criteria included previous Cochrane reviews, as well as previous selective EBM reviews submitted by prior students. This research study analyzed three RCTs. The population in all three studies included women over age 18 who had estrogen receptor-positive, HER2neu negative advanced breast cancer. Two of the three studies, conducted by Finn et al. and Hortobagyi et al., evaluated a CDK 4/6 inhibitor plus anti-estrogen therapy as a first-line systemic treatment for advanced disease, while the other, performed by Cristofanilli and colleagues, included patients who had metastatic breast cancer that progressed on previous endocrine therapy. Palbociclib or ribociclib were representative of CDK4/6 inhibitors, while letrozole or fulvestrant were used for anti-estrogen therapy. Efficacy analysis was performed on the intention-to-treat population and the studies reported numbers needed to treat (NNT), p-values, and confidence intervals (CI). Table 1 shows the demographics and characteristic of the included studies.

The first study by Cristofanilli et al. evaluated 521 women with any menopausal status that had disease progression on previous anti-estrogen therapy. Women who had received a previous CDK inhibitor, fulvestrant, everolimus or a P13K/mTOR pathway inhibitor were excluded. The women were randomly assigned to receive palbociclib plus fulvestrant or placebo plus fulvestrant. Oral palbociclib 125 mg or placebo were administered once daily for three weeks followed by one week off, on a 28-day cycle. Fulvestrant was given to each groups on the following schedule: 500 mg IM injection day 1 and day 15 of cycle 1, then day 1 of each subsequent 28-day cycle. All premenopausal or perimenopausal women had to have started treatment with a luteinizing-hormone-releasing-hormone agonist, goserelin, at least four weeks before randomization. Additionally, during the treatment period, those women received goserelin at the time of fulvestrant administration.

The second RCT by Hortobagyi et al. included 668 postmenopausal women with recurrent or metastatic breast cancer who had not received prior systemic therapy for their advanced disease. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) had to be present or the patients had to have at least one predominately lytic bony lesion. Additional inclusion criteria included an Eastern Cooperative Oncology Group Performance Status of 0 or 1. Patients with inflammatory breast cancer or central nervous system metastasis were excluded. Women were randomly assigned to receive either oral ribociclib plus letrozole or letrozole plus placebo on the following regimens: 1) oral ribociclib 600 mg daily for three weeks, followed by one week off, on a 28-day cycle plus oral letrozole 2.5 mg daily, or 2) oral letrozole 2.5 mg daily plus placebo, and a schedule similar to those receiving ribociclib.

The final RCT by Finn et al. included 165 post-menopausal women who were selected to participate if they had locally recurrent disease not amenable to surgery or evidence of metastatic

disease; those with brain metastasis were excluded. The women were randomly assigned to receive either palbociclib plus letrozole or letrozole alone. The following treatment regimens were followed: 1) oral palbociclib 125 mg, given once daily for three weeks followed by one week off, on a 28-day cycle plus oral letrozole 2.5 mg daily or 2) oral letrozole 2.5 mg daily.

Table 1. Demographics and characteristics of included studies

Study	Type	# pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Cristofanilli[6] (2016)	RCT	521	≥18 yo	Menopausal (natural or medically induced), ECOG 0-1, measurable disease or bone disease only, relapse/progression after previous endocrine therapy during tx or within 12 months, one line of chemotherapy in advanced disease was allowed	Received CDK inhibitor, fulvestrant, everolimus, P13K/mTO inhibitor; extensive symptomatic visceral mets; uncontrolled CNS mets	275*	Fulvestrant 500 mg IM (day 1 & 15 of cycle 1; then day 1 of 28-day cycle) plus oral palbociclib 125 mg (3 out of 4 weeks) vs. fulvestrant IM plus placebo
Finn[4] (2015)	RCT	165	≥18 yo	Post-menopausal, ER+ advanced disease, locally recurrent tumor not amenable to surgery, metastatic disease, measurable tumor by RECIST, adequate organ function	Received letrozole within 12 months, previous systemic treatment for advanced disease, brain mets, previous CDK inhibitor	133*	Daily oral letrozole 2.5 mg plus oral palbociclib 125 mg (3 out of 4 weeks) VS. daily oral letrozole
Hortobagyi[7] (2016)	RCT	668	≥18 yo	Post-menopausal, locally HR+ recurrent or metastatic disease, measurable disease per RECIST, one predominant lytic bone lesion	Inflammatory disease, CNS mets, previous CDK inhibitor, previous systemic tx for advanced disease	319*	Ribociclib 600 mg (3 out of 4 weeks) plus letrozole 2.5 mg daily VS. placebo plus letrozole

*W/D due to objective progression or relapse, adverse events, withdrawal of consent, protocol, patient or physician decision, global deterioration of health status, or death

OUTCOMES MEASURED

All three studies primarily assessed morbidity and mortality based on progression-free survival according to RECIST. This criterion defines when tumors in cancer patients improve, stay the same, or worsen during the treatment course.

In the study by Cristofanilli et al., study treatment continued until disease progression, unacceptable toxic effects, withdrawal of consent, or death. Tumors were assessed at baseline by CT, MRI, or both, as well as every 8 weeks (+/- 7 days) for the first year and every 12 weeks thereafter. Patients with only bone lesions had follow-up CT or MRI every 8 weeks during active treatment for the first year, followed by every 12 weeks from the date of randomization. Confirmation of complete response was also performed. To measure progression-free survival, an audit approach with random sample-based, masked, independent central review was used.[6] In the study by Finn et al., tumor assessments were done by CT or MRI of chest, abdomen, and pelvis at screening and every 8 weeks thereafter. Bone scans were performed, if applicable, at baseline and then every 12 weeks. Progression-free survival was defined as time to radiological disease progression from randomization or death on the study.[4] Hortobagyi et al. assessed tumor response by CT or MRI at screening, every 8 weeks during the first 18 months, and every 12 weeks thereafter until disease progression, as well as at the end of treatment. An independent review committee whose members were unaware of treatment assignments prospectively reviewed all imaging data.[7]

RESULTS

The three RCTs evaluated in this selective review assessed the role of CDK4/6 inhibitors in the treatment of advanced breast cancer. Cristofanilli et al. conducted a multicenter, double-blind RCT that randomly assigned 521 women that progressed on previous endocrine therapy to

either receive fulvestrant plus palbociclib (n=347) or fulvestrant plus placebo (n=174). Administration schedule discussed in detail above. Assignments were made between October 7, 2013 and August 26, 2014 and overall survival follow-up is ongoing. By March 16, 2015, 259 progression-free survival events had occurred, 145 in the palbociclib group and 114 in the placebo group.[6] In the palbociclib group, median progression-free survival was 9.5 months (95% CI 9.2-11.0), compared to 4.6 months (95% CI 3.5-5.6) in the control group.[6] Best overall tumor response for all participants was also assessed, and is described in Table 2 below. Clinical benefit, defined as complete response plus partial response plus stable disease $\geq$ 24 weeks, was evaluated in both groups.[6] Of the 347 subjects in the treatment group, 231 were identified as having clinical benefit, while 69 out of the 174 participants in the control group had the same classification.[6] Absolute benefit increase for this study was 27% and numbers needed to treat (NNT) equated to 4, with p-value statistically significant at <0.0001. Safety assessment included patients who received at least one dose of study drug. The most common side effect in the palbociclib group was neutropenia of any grade, occurring substantially more frequently than in the control group at 81% and 3%, respectively.[6] Additionally, infection, fatigue, nausea, other blood dyscrasias, rash, and alopecia were more common in the palbociclib group. Serious adverse effects accounted for a dose interruption in 54% of the treatment group versus 6% in the placebo group.[6] No deaths related to treatment toxicity occurred in either group. All subjects were accounted for at the conclusion of the trial.

Table 2. Efficacy of Combination Therapy as Measured by Cristofanilli et al. 2016

		Fulvestrant plus palbociclib		Fulvestrant plus placebo	
Clinical benefit*		67%		40%	
95% Confidence Interval		61.3-71.5		32.3-47.3	
Treatment effect					
CER	EER	RBI	ABI	NNT	p-value
0.40	0.67	0.675	0.27	4	<0.0001

*Clinical benefit in the intention-to-treat population is defined by complete response plus partial response plus stable disease equal to or more than 24 weeks

Between December 22, 2009 and May 12, 2012, Finn et al. randomly assigned 165 women to receive palbociclib plus letrozole (n=84) or letrozole alone (n=81). At the time of final analysis, 41 progression-free events occurred in the treatment group, versus 59 in the control group.[4] Median progression-free survival was 20.2 months (95% CI 13.8-27.5) and 10.2 months (95% CI 5.7-12.6), respectively.[4] Of note, a greater proportion of patients had an objective response to treatment and achieved clinical benefit in the palbociclib plus letrozole group compared to those receiving only letrozole.[4] This study also assessed overall survival at the time of the final progression-free survival interval. In the palbociclib group, median overall survival was 37.5 months (95% CI 28.4-NE) and 33.3 months (26.4-NE) in the letrozole group (HR 0.813, 95% CI 0.492-1.345; two-sided p=0.42).[4] Similar to the other two studies, the most common adverse effect in those receiving palbociclib was neutropenia. All patients who received palbociclib plus letrozole had an adverse event, including leukopenia and fatigue, compared to 84% of patients who received letrozole alone; dose interruptions were required for 33% of the combination group, compared to only 4% of the letrozole group.[4] Despite the increase in adverse events in the treatment group, this accounted for only 13% of discontinuation from the study, versus 2% in the control group.[4] Most discontinuations were secondary to progression of disease and were more common in the patients receiving monotherapy, accounting for 70% of patients in that group, versus 50% of patients on combination therapy.[4]

Table 3. Progression-free Survival with Combination Therapy vs Anti-estrogen Monotherapy as Measured by Finn et al. 2016

	Palbociclib plus letrozole	Letrozole alone
Median progression-free survival	20.2 months	10.2 months
95% Confidence Interval	13.8-27.5	5.7-12.6
Treatment effect		
Hazard ratio	0.488	
95% Confidence interval	0.319-0.748	
One sided p-value	0.0004	

In the trial by Hortobagyi and colleagues, from January 24, 2014 to March 24, 2015, 668 post-menopausal women were randomly assigned to receive ribociclib plus letrozole (n=334) or placebo plus letrozole (n=334) for first-line treatment of their recurrent or metastatic breast cancer. Treatment regimens are noted above. By January 29, 2016, 349 patients were still receiving treatment, 195 in the ribociclib group and 154 in the placebo group.[7] Of those that discontinued treatment, progressive disease accounted for the reason in 26% of the ribociclib group, versus 154 in the control group. For this study, a pre-specified interim analysis was conducted when at least 211 patients progressed or died. It should be noted that the median duration of progression-free survival was not reached in the ribociclib group, but was 14.7 months in the placebo group. After 18 months, however, progression-free survival was 63% (95% CI 54.6-70.3) and 42.2% (34.8-49.5), respectively.[7] These results were supported by blinded central analysis. With the end-point of progression-free survival at 18 months, ABI is 20.8% with NNT=5. Similar to the study conducted by Cristofanilli discussed above, safety analyses were evaluated in those patients that received at least one dose of a study regimen; patients were also required to have at least one safety assessment after baseline. Dose adjustments were permitted to manage treatment-related adverse reactions secondary to ribociclib but not for letrozole. Neutropenia was the adverse event leading to the most dose reductions in the ribociclib group (n=104). This effect was not observed in patients receiving placebo.

Table 4. Efficacy of Ribociclib Plus Letrozole as Measured by Hortobagyi et al. 2016

		Ribociclib group		Placebo group
Progression-free survival at 18 months		63%		42.2%
95% Confidence Interval		54.6-70.3%		34.8-49.5%
Treatment effect				
CER	EER	RBI	ABI	NNT
0.422	0.62	0.493	0.208	5

DISCUSSION

As previously discussed, breast cancer is a common malignancy effecting over 3 million women in the United States. Treatment regimens for those with advanced disease are limited, with no known cure available at this time. While endocrine therapy, surgery, radiation, and chemotherapy offer some improvement in survival, drugs that target specific signaling pathways must be considered as an alternative treatment option in patients at advanced stages of malignancy. The study by Cristofanilli et al. showed an improvement in progression-free survival, objective response, and clinical benefit in participants that received fulvestrant plus palbociclib. This study evaluated the use of combination therapy in patients who failed previous treatment, and the benefit was observed regardless of home many prior endocrine therapies they had tried. Additionally, the level of expression of estrogen and progesterone receptors did not significantly alter the above results.[6] Hortobagyi's and Finn's analyses also showed the addition of ribociclib or palbociclib to letrozole improved time until progression when initiated as first-line management for advanced breast cancer. Finn's research also demonstrated clinically significant benefit with combination therapy despite the patient's menopausal status prior to receiving treatment. A limitation to all studies was that dose reductions were necessary in a higher proportion of the treatment group. Although the use of these novel agents is associated with an increased risk of myelosuppression, the adverse events were manageable, and did not appear to have a significant effect on the primary end-point for the studies. The above data suggest that there is an important clinical role for the use of cyclin dependent kinase inhibitors in the management of breast cancer.

CONCLUSIONS

This systematic review showed that the use of CDK4/6 inhibitors in combination with anti-estrogen therapy improves progression-free survival in women with hormone receptor-positive, HER2neu negative advanced breast cancer compared to anti-estrogen therapy alone. Clinical benefit was seen in all three studies irrespective of the choice of combination therapy used. Finn and Hortobagyi described the role of CDK 4/6 inhibition plus anti-estrogen as a first-line treatment option, while Cristofanilli found the combination regimen to also be effective in those who had progressed on previous endocrine therapies. For future studies regarding the use of CDK 4/6 inhibitors, it would be beneficial to have a better understanding of the long-term effects of prolonged use, specifically related to myelosuppression and bone marrow toxicity. Finn addressed the question regarding efficacy in premenopausal as well as postmenopausal women. This inclusion criterion could extend to future studies to increase generalizability of the patient population.

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