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Review Article

The Use of Cyclin-Dependent Tyrosine Kinase 4/6 (CDK4/6) Inhibitors in Breast Cancer

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Abstract

Breast cancer has the highest prevalence of all cancers in females, with roughly 2.26 million new cases diagnosed and an estimated 0.68 million deaths/year. Hormone receptor-positive (HR+) or human epidermal growth factor receptor-negative (HER2-) illness affects the vast majority of patients with metastatic breast cancer (MBC). Endocrine therapy (ET) with aromatase inhibitors (AIs) is the preferred first-line choice for this subpopulation. However, because most patients developed tolerance to these medications, demand for alternate endocrine regimens has surged. Inhibition of cyclin-dependent kinase 4 and 6 (CDK4/6) is proving to be a success in resistant patients as well as a first-line treatment. This review article highlights the current indications for CDK4/6 inhibitors in breast cancer that have been approved by the FDA. The literature search was confined to the years 2015 to 2020, and 27 articles and 6 studies were chosen for further research from a large number of publications. In hormone receptor-positive, HR RC+, HER2- advanced or metastatic breast cancer (ABC/MBC) patients, the use of currently available CDK4/6 inhibitors, either alone (abemaciclib) or in combination with endocrine therapy (Palbociclib and Ribociclib), showed a beneficial effect when compared to endocrine therapy alone. The use of CDK4/6 inhibitors resulted in longer progression-free survival (PFS), greater clinical benefit rates (CBR), and an overall response rate (ORR), as well as an overall survival (OS) advantage in patients previously treated with endocrine treatment (ET).

Keywords: Breast cancer; CDK4/6 inhibitors; Endocrine therapy; Pre and post-menopausal women.

استخدام مثبطات التيروسين كيناز المعتمدة على السيكلين (CDK4/6) في سرطان الثدي

الخلاصة

لسرطان الثدي أعلى معدل انتشار بين جميع أنواع السرطان في الإناث، مع ما يقرب من 2.26 مليون حالة جديدة تم تشخيصها وما يقدر بنحو 0.68 مليون حالة وفاة/سنة. يؤثر مرض مستقبلات الهرمونات الإيجابية (HR+) أو مستقبلات عامل نمو البشرة البشرية السلبية (HER2-) على الغالبية العظمى من المرضى الذين يعانون من سرطان الثدي النقلي. علاج الغدد الصماء (ET) مع مثبطات الأروماتيز (AIs) هو الخيار الأول المفضل لهذه الفئة الفرعية. ومع ذلك، نظراً لأن معظم المرضى اضهروا تحملاً لهذه الأدوية، فقد ارتفع الطلب على أنظمة الغدد الصماء البديلة. وقد ثبت أن تثبيط الكيناز 4 و 6 المعتمد على السيكلين (CDK4/6) نجح في المرضى المقاومين بالإضافة إلى علاج الخط الأول. تسلط هذه المقالة الضوء على المؤشرات الحالية لمثبطات CDK4/6 في سرطان الثدي التي تمت الموافقة عليها من قبل إدارة الأغذية والعقاقير الأمريكية. اقتصر البحث في الأدبيات على السنوات من 2015 إلى 2020، وتم اختيار 27 مقالة و 6 دراسات لمزيد من البحث من عدد كبير من المنشورات. في مرضى سرطان الثدي المتقدم أو النقلي المصابين بمستقبلات الهرمونات أو HR RC+ أو HER2، أظهر استخدام مثبطات CDK4/6 المتاحة حالياً، إما بمفردها (abemaciclib) أو بالاشتراك مع علاج الغدد الصماء (Palbociclib و Ribociclib)، تأثيراً مفيداً عند مقارنته بعلاج الغدد الصماء وحده. أدى استخدام مثبطات CDK4/6 إلى زيادة معدلات الفائدة السريرية، ومعدل استجابة إجمالي، بالإضافة إلى ميزة البقاء على قيد الحياة بشكل عام في المرضى الذين عولجوا سابقاً بالأدوية المؤثرة على الغدد الصماء.

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INTRODUCTION

With nearly 2.26 million new cases diagnosed and an estimated 680,000 deaths per year, breast cancer (BC) has had the highest prevalence of all cancers in females. So it is a global health crisis for women, and it is also the most common type of non-skin cancer worldwide [1]. It is a group of various biological and molecular diseases that can be originated in different areas of the breast [2]. Almost all begin in the cells that line the ducts (ductal cancer), a few begin in the cells that line the lobules (lobular cancers), and then a smaller number originates in the other tissues [2]. So it is important to distinguish between these different subtypes since each type has its unique prognosis and treatment strategy. Breast cancer could be classified according to tumor size, histologic subtype, tumor grade, the extent of vascular invasion, nodal involvement, hormone receptor status, and expression of HER2, Ki67, and p53 [3]. DNA microarray profiling studies on breast tumors have identified five distinct subtypes of breast cancer which include: luminal A (ER+, PR+, HER2- with low level of protein ki-67, and low grade), luminal B (ER+, PR+/-, HER2+/-, high level of ki-67, and high grade), HER2 overexpressing (ER-, RC-, HER2+, high grade), basal-like also called triple-negative (HR RC-, HER2- with a high level of ki-67, and high grade) as well as normal breast-like BC [4]. The majority (about 75%) of patients with MBC have HR+/HER2- disease. For this subgroup, the use of aromatase inhibitors (AIs) is the preferred first-line treatment option. However, resistance to these treatments develops in most patients, requiring the administration of sequential therapy with alternative endocrine regimens. It is therefore important to identify successful alternative therapies that extend or restore sensitivity to endocrine therapies [5,6]. Preclinical data have shown that proliferation induced by estrogen receptors requires cyclin D (CCND), which is a regulatory protein that acts both as a catalyst for cyclin (CDK) 4 and 6 and as a transcriptional target of the ER, it is highly expressed in about 50 percent of BC patients [6]. Luminal tumors are especially enriched by amplification of CCND1 and/or gain of CDK4 [7]. Over activation of CDK 4 and 6 can reduce senescence and promote progression of the cell cycle, therefore CDK 4 and 6 inhibitions is proving to be an effective strategy in resistant patient and also as a first-line agent [5,8]. CDK4/6 and CCND interactions closely regulate the G1/S control point of the cycle of the cell [9]. CDK4/6 interacts with cyclin D in the G phase of the cell cycle to form the cyclin D-CDK4/6 complex that phosphorylates Rb a tumor suppressor protein, which binds closely to the E2F transcription factor before phosphorylation, after phosphorylation it will release E2F from the Rb-E2F complex, which is followed by upregulation of the target genes of E2F and initiation of DNA synthesis, leading to entry into the S phase of the

cell cycle. In BC cell lines, CCND induction initiates the cell cycle process and increases the percentage of cell processing phases from G1 to S by several genetic and epigenetic mechanisms [8,10]. It has been found that ET prevents this pathway's activation, while CDK4/6 selective inhibitors induce G1 arrest and decrease Rb protein phosphorylation, with subsequent down-regulation of E2F downstream effectors [9,10]. Inhibition of CDK4/6 may also change the metabolism of cells, deplete antioxidants, increase ROS and cause apoptosis, and influence both the maturation of sentinel cells in the immune system and the expansion of regulatory cells [7,11] (Figure 1).

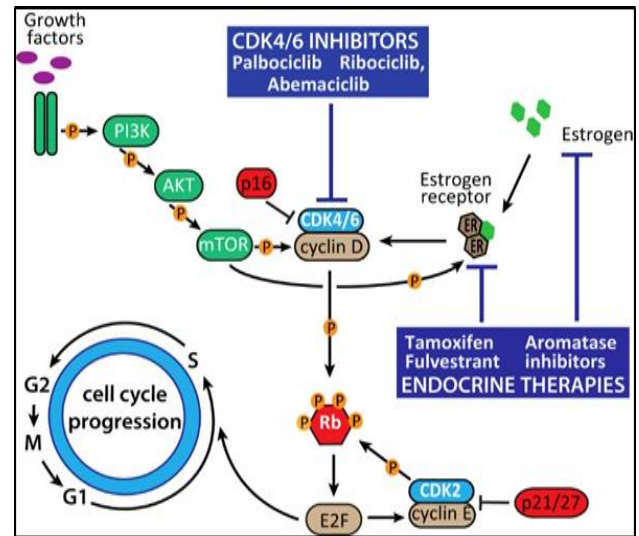


Figure 1: The mechanism of action of CDK4/6 inhibitors [11].

Palbociclib was the first inhibitor of CDK4/6 to show clinical efficacy, soon followed by two others, Ribociclib, and abemaciclib. Ribociclib is somewhat similar to Palbociclib in structure, and abemaciclib is slightly less similar to either of the two [7]. All three inhibitors of CDK4/6 are available as oral dosage forms, but each has different pharmacokinetics and clinical toxicities, requiring various dosing strategies. Ribociclib and Palbociclib are both administered once daily, while abemaciclib is administered twice daily [7]. Ribociclib is noteworthy for its long half-life (greater than 30 hours) of reaching high maximum plasma concentrations (greater than 2 µg/mL) [7,8]. For reasons that are not entirely obvious, there are marked variations in their toxicity profiles; grade 3-4 neutropenia is found in approximately 60 percent of patients taking Palbociclib and Ribociclib. With only 55 percent of patients reporting serious adverse events (compared to 70-80 percent with Ribociclib and Palbociclib) and only 21 percent with neutropenia, grade 3-4 abemaciclib tends to be better tolerated overall [7]. The clinical trials on CDK4/6 inhibitors begin 5 years ago and the outcome of these researches provided us with new approaches for treating women with BC either alone or in

conjunction with endocrine therapy in women with HR RC+/HER2- breast BC, as neoadjuvant or adjuvant therapy in the same setting, as well as in HER2+ and triple-negative BC. The later three indications of CDK4/6 inhibitors are still under investigation and further head-to-head phase 3 clinical trials are needed to confirm their biological and clinical activity. This review article will concentrate on the existing indication of CDK4 inhibitors in breast cancer that has been approved by the FDA.

METHODS

A precise article review focusing on the current role of CDK4/6 inhibitors in the treatment of breast cancer. The google and google scholar databases, PubMed, and the scientific cancer journals were searched and the reference lists of the relevant article were included. The following keywords were used: breast cancer, breast cancer subtypes, the role of inhibitors of CDK4/6 in breast cancer, the mechanism of action of CDK4/6 inhibitors, and CDK4/6 inhibitors indication in breast cancer. The research was limited to the period from 2015 to 2020 and from a lot of articles and studies, 26 articles and 6 studies were chosen for further analysis depending on the inclusion and exclusion criteria of the review article (Figure 2).

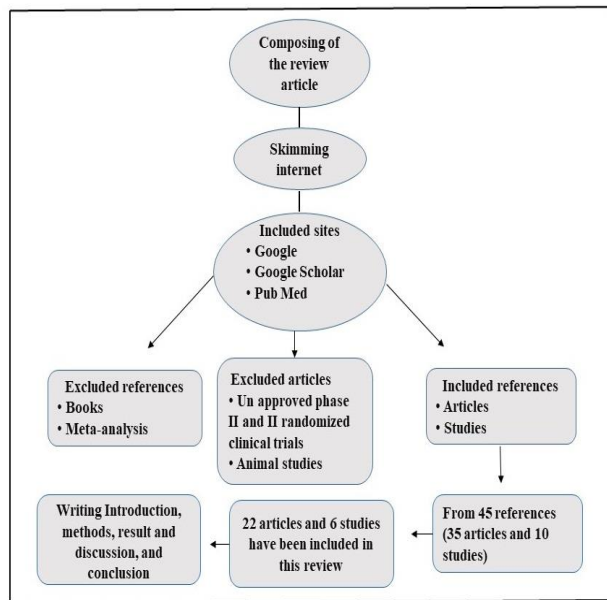


Figure 2. Flow chart of the study.

RESULTS AND DISCUSSION

Firstly, Palbociclib has gained accelerated approval in conjunction with AIs for first-line care of postmenopausal women with HR RC+/HER2- ABC. The approval was based on the findings of Phase 2 PALOMA-1 randomized controlled trial (RCT), which showed a significant increase in median progression-free survival (PFS) in the

Palbociclib plus letrozole arm compared to letrozole alone arm [12,13] (Table 1). Paloma-1 was fully accessible and did not use a central radiology analysis to test the primary endpoint prospectively, and this was the limitation of the study [12,13]. One year later the result of PALOMA1 was confirmed by PALOMA-2 phase 3 randomized controlled trial (RCT), which also showed a significant increase in the median PFS, CBR, and ORR [14]. In combination with fulvestrant for MBC based on evidence from the PALOMA-3 trial in pre/postmenopausal ER+/HER2-ABC who had progressed on ET (either tamoxifen or AIs) Palbociclib also showed a total prolongation of 6.9 months of overall survival (OS) and an increase in the median PFS from (4.6 -9.5) months which was different in Asian patient [15,16] (Table 1). Interestingly Palbociclib indication was extended by the FDA to male patients with HR+/HER2-mBC, and this approval was based on real-world evidence from electronic health records in 2019 [17]. In premenopausal women with HR RC+/HER2- MBC that had relapsed or progressed during previous tamoxifen therapy in terms of improved PFS, Palbociclib plus Exemestane and ovarian function suppression showed clinical benefit relative to Capecitabine, according to the results obtained from young PERAL phase 2 RCT [18]. Whereas in postmenopausal women with HRRC+/HER2- MBC whose disease also progressed on AIs, the PEARL study did not reveal any statistical superiority in PFS for Palbociclib + ET (Exemestane first then Fulvestrant) versus Capecitabine till now [19]. Similarly, Ribociclib was approved by the FDA in conjunction with AIs as initial therapy for treating postmenopausal women with (HR+/HER2-) early BC before or during surgery, based on evidence from MONALEESA-1 phase 2 RCT (which was limited by few patient numbers and short therapy duration) and in postmenopausal women with (HR+/HER2-) recurrent or ABC according to MONALEESA-2 phase 3 RCT (which was limited by 43 fatalities at the time of the cutoff of data, 20 patients in the placebo group and 23 patients in the Ribociclib group, and therefore it was blinded for overall survival follow-up). Both MONALEESA-1 and MONALEESA-2 showed an increase in ARR and median PFS respectively [20,5]. Also Ribociclib in conjunction with fulvestrant as first or second-line treatment in postmenopausal women ER+/HER2- ABC who were TN or had earned up to one previous line of ET was approved by FDA according to the evidence from MONALEESA-3 phase 3 RCT, which show a significant increase in the PFS. This study was restricted by a limited number of patients, which precludes the conclusion about pharmacokinetics, pharmacodynamics, and biomarker assessment, and a short period of therapy which could affect its accuracy [21,22]. Furthermore, the MONALEESA-7 phase III

study investigate Ribociclib in conjugation with ET and Goserelin in premenopausal women who receive only one previous chemotherapy line without previous ET, the result was a significant prolongation in both PFS and OS and HR+/HER2- ABC patients, and after 192 deaths (24.8 percent in the Ribociclib arm and 32.3 percent in the placebo arm) the average survival in the Ribociclib group was slightly longer than the placebo group, with 29 percent reduction in the risk of death in a patient with HR+/HER2- ABC [23,24] (Table 1). Abemaciclib safety and efficacy as a single agent in women with HR+/HER2-MBC whose disease progressed on or after ET and CT were evaluated in phase II single-arm study MONARCH-1 RCT, which showed an overall response rate (ORR) of 19.7%, CBR of 42.4%, and median PFS of 6.0 months [25]. The findings of MONARCH 2 phase III RCT testing abemaciclib in combination with fulvestrant in postmenopausal women with ER+/HER2- BC who had progressed to neoadjuvant ET or ABC, showed a substantial improvement in PFS compared to placebo plus fulvestrant in the control arm. Patients received abemaciclib at a dose of 200 mg twice daily at the start of the study, then changed to 150 mg twice daily for safety intentions. At the time of the data cut-off, the overall survival (OS) results were still not complete, with 85 deaths in the abemaciclib arm (19.1 percent) and 48 (21.5 percent) in the placebo arm [6]. The same result (significant improvement in PFS and ORR) was obtained from MONARCH-3 RCT which evaluates the efficacy of abemaciclib plus non-steroidal AIs (either anastrozole or letrozole) versus placebo plus AI in postmenopausal women with HR+/HER2- ABC who had no previous systemic therapy [26,27]. Finally, MONARCH plus phase 3 RCT predominantly in Chinese postmenopausal women with HR RC+/HER2- ABCC showed a statistically

relevant and clinically significant improvement in PFS [28] (Table 1).

Conclusion

A new approach has emerged in the historical timeline of luminal ABC care with CDK4/6 inhibitors. In HR RC+/HER2- ABC/MBC patients with CDK4/6 inhibitor progress. Longer PFS and higher CBR as well as ORR were obtained. In patients previously treated with ET, the advantage of OS was also reported. CDK4/6 inhibitors are a highly worthy treatment choice for breast cancer patients with their effectiveness, low and manageable toxicity, and oral dosage route availability. However, a head-to-head comparative analysis that helps us to differentiate between the various options available of CDK4/6 inhibitors, and to evaluate their activity in HER2-positive or triple-negative BC is deemed significant. This review article highlighted the existing indication of CDK4 inhibitors in breast cancer that has been approved by the FDA

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Conflict of interests

The author declares no conflict of interests.

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Data sharing statement

N/A

Table 1: Phase 2 and phase 3 randomized clinical trials on the currently available CDK4/6 inhibitors

Study and design	Selected treatment	Treatment doses	Median follow-up (months)	Primary endpoint	Secondary endpoints	Grade 3/4 AE
PALOMA-1 phase 2 (open label) [12,13]	Palbociclib + letrozole vs. Letrozole (n=165) 1 st line	125 mg 3/4w +2.5mg vs. 2.5 mg	29.6, 27.9	mPFS 20.2 m vs. 10.2 m	mDR, mOS 20.3, 37.5 vs. 11.1, 34.5	Neutropenia, Pulmonary embolism, Back pain, Diarrhea
PALOMA-2 phase 3 (double-blind) [14]	Palbociclib +letrozole vs. Letrozole (n=666) 1 st line	125 mg3/1w+2.5 mg/d vs. 2.5 mg/d	23	mPFS 24.8 vs. 14.5 m	CBR, ORR 84.9%,42.1% vs. 70.3%, 34.7%	Neutropenia
PALOMA-3 phase 3 (double-blind) [15,16]	Palbociclib + fulvestrant vs. fulvestrant + placebo (n=521) 1 st 25%, 2 nd 39%, others 36%	125 mg 3/4w+500 mg vs. 500 mg	8.9, 44.8	mOS 34.9 vs. 28	PFS 9.5 vs. 4.6 (5.8 in Asian patients)	Neutropenia, Leukopenia, Fatigue, Nausea
young PEARL (open-label) [18]	Palbociclib + oral Exemestane P.O + Leuprolide vs. Capecitabine (n=178) 1 st line or 2 nd line	125/d,3/1w off + 25 mg/d + 3.75 mg SC vs. 1250 mg/m2 BID/2w repeated every 3w	17	PFS 20.1 vs. 14.4		Neutropenia, Leukopenia, Anemia, Microsites, Nausea, Diarrhea.

PEARL –phase 3 (open label) [19]	Cohort 1: Exemestane + Palbociclib vs. Capecitabine Cohort 2 Fulvestrant + Palbociclib vs. Capecitabine (n=601) 1 st or 2 nd line		19.0 (range 0.0-56.3), 13.5 (range 0.0-30.7)	PFS 8 vs. 10.6; 7.5 vs. 10	ORR 27.8% vs. 36.9%; 26.7% vs. 33.3%	Febrile neutropenia, Hand/foot syndrome, Diarrhea.
MONALEESA-1 [20]	Ribociclib + Letrozole vs. Letrozole (n=14) 1 st line	400 mg/d and 600 mg/d + 2.5 mg/d vs. 2.5 mg/d	9.2	AAR/Ki67 96% and 92% vs. 69%		N/D
MONALEESA-2 phase 3 (double blind) [5]	Ribociclib + letrozole vs. letrozole + placebo (n=668) 1 st line	600 mg/d/3/4w + 2.5 mg vs. 2.5mg	15.3	PFS 23 vs. 21	ORR, CBR 52.7, 79.6 vs. 37.1, 72.8	Neutropenia, Leukopenia, Hypertension, Lymphocytopenia, Increased AST, Infection.
MONALEESA-3 (double-blinded) [21,22]	Ribociclib 600 mg/d,3/1w off) + fulvestrant vs. Placebo + Fulvestrant (n=484) 1 st or 2 nd line	600 mg/d, 3/1w off + 500 mg IM/IV vs. 500 mg	20.4, 39.4	PFS 20.5, 33.6 vs. 12.8, 19.2	OS 57.8% vs. 45.9%	Elevate ALT, AST, Pneumonia, dyspnea.
MONALEESA-7 phase 3 double blind [23,24]	Ribociclib + Tamoxifen or AIs either Letrozole or Anastrozole + Goserelin vs. Placebo + ET + Goserelin (n=672) 1 st or 2 nd line	600 mg/d,3/1w off + (20 mg or + 2.5 mg/d or 1 mg/d) + 3.6 mg/28 d vs. x + same doses	19.2, 34.6	PFS 23.8 m vs. 13 m	OS 70.2% vs. 46%	Neutropenia, Leucopenia, Prolonged QT interval, Hepatobiliary toxicity.
MONARCH-1 single-arm [25]	Abemaciclib (n=123) 2 nd line	200 mg BID	10	mPFS 6 m	ORR 19.7%; CBR 42.4%	Diarrhea, Fatigue, Nausea, Decreased appetite, and Abdominal pain.
MONARCH-2 (double blind) [6]	Abemaciclib + Fulvestrant vs. Fulvestrant + Placebo (n=669) 1 st line	150 mg BID + 500 mg vs. 500 mg	19.5	PFS 16.4 vs. 9.3	ORR, CBR 48.1, 72.1 vs. 21.3, 56.1	Diarrhea
MONARCH-3 (double-blind) [26,27]	Abemaciclib + NSAI (either Anastrozole or Letrozole) vs. Placebo + NSAI (n=493) 1 st line	150 mg BID + (1 mg or 2.5 mg) vs. 1 mg or 2.5 mg	17.8, 26.7	mPFS 28.18 vs. 14.76	ORR 49.7% vs. 37%	Neutropenia, Diarrhea, and Leukopenia.
MONARCH plus phase 3 (double-blind) [28]	Cohort A: Abemaciclib + NSAI (anastrozole or letrozole) vs. Placebo + NSAI; Cohort B: Abemaciclib + Fulvestrant vs. Placebo + Fulvestrant. (n= 463, 306 vs. 157) 1 st line	150 mg BID		PFS A: NR vs. 14.73; B: 11.47 vs. 5.59	ORR A: 56 vs. 30.3; B: 38.5 vs. 7.5	

n: sample size; OS: overall survival; ORR: overall response rate; PFS: progression-free survival; NR: no response; CBR: clinical benefit rate.

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