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REVIEW

Advancements in Dalpiciclib for the Treatment of Breast Cancer Patients: A Review

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Abstract: Combining cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6 inhibitors) with cyclin-dependent proteins can reduce the formation of cyclin D-CDK4/6 complexes, resulting in the inactivation of downstream genes and suppression of cell proliferation. Previous research on the use of CDK4/6 inhibitors in combination with endocrine therapies and anti-HER2 targeting agents across various subtypes and stages of breast cancer has shown promising outcomes in patient prognoses and tolerable drugs toxicities. For the present, the CDK4/6 inhibitors that have been widely used for the treatment of breast cancer are palbociclib, abemaciclib and ribociclib. Dalpiciclib (SHR6390), a novel and selective CDK4/6 inhibitor developed in China, has been approved by the National Medical Products Administration. The researches about dalpiciclib with different anti-tumor drugs are ongoing to explore the efficacy and the best strategies to use dalpiciclib. This review provides an overview of the research progress on dalpiciclib across different breast cancer subtypes with various anti-tumor drugs in different treatment opportunities.

Keywords: breast cancer, dalpiciclib, CDK4/6 inhibitors, cyclin D

Introduction

With more than 2.3 million new cases worldwide, breast cancer was the most frequently diagnosed cancer in 2022 in females, according to estimates by the International Agency for Research on Cancer. A significant portion of these patients were diagnosed at advanced stages. Asia accounts for nearly 50% of new cancer cases and over half of cancer-related mortality, with China representing a substantial proportion.[1] The National Cancer Center of China reported over 4.8 million new cancer cases and more than 2.5 million cancer deaths in 2022. Among these, breast cancer was the second most common cancer and the fifth leading cause of cancer death in females, posing a significant burden.[2] Even after undergoing standardized comprehensive therapies, early breast cancer patients still face a considerable risk of recurrence. A study indicated that the 15-year cumulative recurrence risk for breast cancer patients is 8.5%, with the recurrence rate increasing annually.[3] To prolong disease-free survival and overall survival (OS) in relapsed and advanced breast cancer (ABC) patients, and to improve their quality of life, the combination of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors with endocrine therapy has been recommended as the initial treatment for hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer (MBC) and ABC patients by the National Comprehensive Cancer Network guidelines[4] and the Chinese expert consensus.[5] Recently, an increasing number of anti-tumor drugs have been combined with CDK4/6 inhibitors in pursuit of the most effective anti-tumor strategy.

CDK4/6 Inhibitors

Cell proliferation is divided to five phases (G0, G1, S, G2, M) according to the classical cell cycle model, and the last four phases (G1, S, G2, M) are proliferative phases.[6]

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The cell cycle strictly modulates cell proliferation procedures by a great many of cell cycle regulators to ensure the accuracy of DNA replication. Cyclins and cyclin-dependent kinases are essential regulators that can promote the cell cycle progress, and of them, the cyclin D makes a decisive function in cell entering cell cycle.[7] D-type cyclins comprise cyclin D1, cyclin D2, cyclin D3, encoded by different CCND genes, respectively, and exert different effects in controlling the process of cell cycle. The expression of CCND genes has increased after receiving stimuli from different signaling pathways in the mitosis, and thereupon the cyclin Ds have increased, and the level of cyclin Ds can be also elevated by increasing translation via some signaling pathways, such as the PI3K-Akt-mTOR pathway. CDK 4/6 are activated by Cyclin Ds, and then combined with cyclin Ds to form cyclin D-CDK4/6 complexes.[8–10] Subsequently, the retinoblastoma (RB) protein, a tumor suppressor that is encoded by retinoblastoma tumor suppressor gene, is phosphorylated by cyclin D-CDK4/6 complexes. This phosphorylation of RB protein is a key point to the transition from G1 to S. RB protein combines with E2F transcription factors by a highly conservative region, when RB protein is phosphorylated by cyclin D-CDK complex, the structure of the region is changed, and the E2F is released from the RB protein.[11] Then the cyclin E was activated and bound to CDK2, forming the cyclin E-CDK2 complex. On one hand, this complex phosphorylated the RB protein, reinforcing the preceding process. On the other hand, it activated downstream target genes,[12,13] enabling the cell to pass the G1 phase restriction point and transition to the S phase, thereby promoting cell proliferation and division.[14,15] An imbalance in regulatory factors of the cell cycle, such as the overexpression of cyclin D1 caused by stimuli from different signaling pathways, can lead to uncontrollable phosphorylation of the RB protein, resulting in abnormal cell proliferation and tumor development.[16–18] Overexpression of the cyclin D1 is common in breast cancer patients[19,20] and the cyclin D1 overexpression or CCND1 amplification has also strengthen tumor invasiveness which indicated worse prognosis.[21–24] The cyclin D1-CDK4/6 complex is crucial for maintaining tumor cell proliferation, while the absence of one of CDK4, CDK6 or cyclin D1 does not significantly affect normal mammary gland cell development.[25,26] Therefore, CDK4/6 inhibitors have been developed to inhibit CDK4/6 activity, preventing their binding to the cyclin D protein. This decreases the formation of the cyclin D-CDK4/6 complex, prevents RB protein phosphorylation, downregulates E2F transcription factor expression, halts the cell cycle, and inhibits tumor growth. Additionally, CDK4/6 inhibitors can block tumor growth by regulating mitotic kinase, inducing a senescence phenotype by motivating anti-tumor activation, and enhancing tumor immunogenicity.[27–29]

Recently, several CDK4/6 inhibitors, including palbociclib, ribociclib, abemaciclib, and dalpiciclib, have been approved for the treatment of breast cancer.

The PALOMA-2 trial, which compared palbociclib plus letrozole to placebo plus letrozole in HR+/HER2- ABC, showed a significant improvement in median progression-free survival (mPFS),[30] Besides, the PALOMA-3 showed an OS improvement.[31,32] However, the follow-up overall survival (OS) data did not achieve expected results.[33] The PALLAS trial,[34] which evaluated palbociclib in combination with endocrine therapy versus endocrine therapy alone in HR+/HER2- early breast cancer (EBC), and the Penelope-B Trial[35] both failed to improve invasive disease-free survival (iDFS).

Several combinations of abemaciclib and endocrine therapy (ET), such as with fulvestrant or aromatase inhibitors, have demonstrated increased median OS and PFS compared to placebo plus ET in HR+/HER2- ABC.[36,37] Furthermore, abemaciclib with ET in high-risk HR+/HER2- EBC has shown potential in reducing recurrent risk.[38] The monarcHER trial explored the addition of trastuzumab to abemaciclib, with or without fulvestrant, compared to fulvestrant with chemotherapy in HR+/HER2+ ABC. The triple-drug combination successfully extended PFS compared to other groups.[39] However, the concerns about adverse events (AEs) related to abemaciclib persist. In the abemaciclib arm, 45.9% of patients experienced grade ≥3 AEs,[38] 69.4% (237 patients) in the MONARCH 3 trial,[37] and 16.6% (463 patients) discontinued abemaciclib therapy due to AEs in monarchE trial. As for ribociclib, its combination with ET (letrozole, which achieved a median OS of 63.9 months, or fulvestrant, which achieved a median OS of 67.6 months) has provided significant benefits to not only HR+/HER2- ABC patients, regardless of menopausal status,[40–42] but also EBC patients.[43] And the maintenance of ribociclib with ET offered prolonged PFS in HR+/HER2- MBC in patients who had progressed after receiving CDK4/6 inhibitors with ET.[44] Besides, a trial comparing ribociclib plus ET to combination chemotherapy in premenopausal, aggressive HR+/HER2- ABC showed non-inferior response rates, with better PFS and tolerance.[45] A pooled analysis[46] that incorporated data from 3 trials

(MONALEESA-2, −3, −7) revealed neutropenia as the most common adverse event, leading to dose reductions in many patients. However, the reductions typically occurred only once. Overall, trials involving ribociclib have shown positive results in extending PFS and OS. However, these trials primarily focus on HR+/HER2- patients, leaving other BC subtypes to be explored.

Dalpiciclib, the first CDK4/6 inhibitor developed in China, is a highly selective, small-molecule inhibitor.[47] Dalpiciclib inhibits cell proliferation by reducing RB protein phosphorylation and the level of phosphorylated RB protein. It significantly inhibits the proliferation of RB protein-positive tumor cells without showing obvious toxic effects on RB-negative cells. Dalpiciclib has demonstrated similar or better anti-tumor activity compared to other inhibitors, overcomes endocrine resistance, significantly reduces toxicity, and improves the chemotherapy response rate.[48–50] This review will highlight the research progress of dalpiciclib in breast cancer patients of different subtypes.

Research Progress on Dalpiciclib

Dalpiciclib in HR+/HER2- ABC

Based on the promising results from preclinical trials,[48] China conducted the first human clinical trial of dalpiciclib.[49] This trial primarily aimed to assess the drug's tolerance, safety, and antitumor activity at optimal dosing levels. Forty patients with HR+/HER2- ABC who had previously failed standard antitumor therapies were enrolled, with dalpiciclib doses ranging from 25 mg to 175 mg. In the 150 mg dose cohort, 80% [95% Confidence interval (CI): 44.7–97.5%] achieved disease control, with a median progression-free survival (mPFS) of 8.4 months (95% CI: 2.1 - not met). The most common grade 3/4 adverse events (AEs) were hematological toxicities, including neutropenia and leukopenia, affecting 22 participants (55%). No serious adverse events (SAEs) or grade 5 AEs were reported, and no subjects discontinued dalpiciclib due to AEs or SAEs. These findings underscore dalpiciclib's efficacy, manageable toxicity, and optimal oral dosing regime, forming a foundation for further clinical trials.

The DAWNA-1 study,[51] a multicenter, randomized clinical trial, compared the efficacy and safety of dalpiciclib plus fulvestrant against a placebo plus fulvestrant. This study enrolled 361 HR+/HER2- ABC patients who had relapsed and progressed following first-line endocrine therapy. All participants had received at least one prior endocrine therapy. Interim analysis demonstrated that patients receiving dalpiciclib plus fulvestrant (240 patients) had a significantly longer mPFS of 15.7 months (95% CI: 11.1 months – not reached) compared to 7.2 months (95% CI: 5.6 months - 9.2 months) for those on placebo plus fulvestrant, with a hazard ratio of 0.42 (95% CI: 0.31–0.58; one-sided $P < 0.0001$). At 6 months, the PFS rates were 76.4% (95% CI: 70.1–80.5%) for the dalpiciclib group versus 53.2% (95% CI: 43.5–62.0%) for the placebo group. At 12 months, the rates were 51.8% (95% CI: 43.2–59.8%) versus 29.1% (95% CI: 20.2–38.5%), respectively.

The DAWNA-2 study[52] evaluated the efficacy of dalpiciclib combined with aromatase inhibitors (letrozole or anastrozole) versus placebo with aromatase inhibitors as first-line therapy for HR+/HER2- ABC patients. This placebo-controlled study enrolled 456 patients across 42 hospitals in China, with 303 patients in the dalpiciclib plus aromatase inhibitors group and 153 in the placebo plus aromatase inhibitors group. Results indicated that, regardless of menstrual status, the mPFS for the dalpiciclib plus aromatase inhibitors group was significantly longer than for the placebo group [30.6 months (95% CI: 30.6 - not reached) versus 18.2 months (95% CI: 16.5–22.5); stratified hazard ratio: 0.51 (95% CI: 0.38–0.69); one-sided $P < 0.0001$].

The findings from both DAWNA-1 and DAWNA-2 suggest that dalpiciclib, when combined with endocrine therapy (either aromatase inhibitor or fulvestrant), offers significant benefits for HR+/HER2-ABC patients, both as a first-line treatment or beyond. The studies indicate a notable reduction in tumor size and a significant prolongation of PFS, thus affirming dalpiciclib's potential as a valuable therapeutic option in this patient population. However, both studies included populations exclusively from China. Due to the heterogeneity of breast cancer across different ethnicities, the benefits for other non-Asian populations remain unclear. Additionally, the overall survival data are still immature. Currently, a large-scale study on dalpiciclib is underway.

Dalpiciclib in Triple-Positive Breast Cancer (TPBC)

The LORDSHIPS study[53] was a single-center, dose-seeking clinical trial that recruited 15 postmenopausal patients with distant metastatic TPBC. The study evaluated the efficacy of dalpiciclib combined with pyrotinib and letrozole. Results showed tumor shrinkage in 14 patients, with 10 achieving a partial response, yielding an objective response rate (ORR) of 66.7% and an mPFS of 11.3 months. This study demonstrated that the combination regimen of dalpiciclib, pyrotinib, and letrozole had a significant anti-tumor effect in postmenopausal patients with distant MBC.

Building on these results, the MUKDEN 01 study[54] was conducted. This single-arm clinical study recruited 81 participants with stage II or III TPBC to assess the efficacy and safety of pyrotinib, letrozole, and dalpiciclib as a neoadjuvant therapy strategy. The primary endpoint was achieving a pathological complete response (pCR) in both the breast and axilla. Secondary endpoints included Residual Cancer Burden (RCB-0/1), ORR, breast pathologic complete response (bpCR) rate, safety, and changes in Ki 67% (a tumor proliferation antigen). Among the 79 patients analyzed, 24 (30.4%, 95% CI: 21.3–41.3%) achieved pCR in both the breast and axillary lymph nodes, and 28 (35.4%, 95% CI: 25.8–46.5%) achieved bpCR. The ORR was 87.4% (95% CI: 78.1–93.2%), and the average Ki 67% decreased from 40.4% to 17.5%.

The combination regimen of dalpiciclib, pyrotinib, and letrozole in the LORDSHIPS and MUKDEN 01 studies showed significant benefits for TPBC patients, likely due to the extensive interaction between HER2 and estrogen receptor (ER) signaling pathways. Anti-HER2 targeted therapy can lead to the redistribution of ER in the nucleus, activating the ER signaling pathway,[55] which can confer resistance to tamoxifen in some patients. Dalpiciclib can partially inhibit this ER pathway activation caused by anti-HER2 targeted drugs, thereby enhancing the anti-tumor effect. However, the three-drug combination regimen did not achieve high rates of pathological complete remission in the breast and axillary lymph nodes.

Recently, a pilot trial (MUKDEN 01 Plus[56]) added trastuzumab to the three-drug combination regimen as a new adjuvant therapy for stage II or III TPBC patients. Among the 12 patients enrolled, 7 achieved pCR in both the breast and axillary lymph nodes after treatment, with an RCB0/1 rate of 75% (95% CI: 46.8–91.1%) and an ORR of 92% (95% CI: 64.6–98.5%). The average Ki 67% decreased from 45.0% (95% CI: 19.5–70.5%) to 17.2% (95% CI: 0.7–33.7%). This four-drug combined neoadjuvant therapy regimen demonstrated excellent pCR rates, but the small sample size and the short follow-up time limit the strength of these findings. Additionally, the safety profile of the four-drug combination was not discussed, necessitating further trials to validate these results. The three-drugs regimen in MUKDEN 01 study has showed great ORR as neoadjuvant therapy, maybe it can increase breast conservation rate.

Dalpiciclib in HER2+/ HR Negative (HR-) ABC

The DAP-HER-01 study[57] investigated the combination of dalpiciclib and pyrotinib in patients with HER2+ ABC who had not previously received anti-HER2 or CDK4/6 inhibitors. The efficacy analysis included 40 participants, of whom 22 were HR-. The results indicated an overall mPFS of 11 months (95% CI: 7.3–19.3).

Post-hoc exploratory analysis showed that HR- patients had a higher ORR compared to HR+ patients, with ORRs of 81.8% (95% CI: 59.7–94.8%) and 55.6% (95% CI: 30.8–78.5%), respectively. Additionally, the median time to disease progression was longer in trastuzumab-sensitive participants than in trastuzumab-resistant participants. Perhaps, it is related that some ER+ (estrogen receptor positive) patients will induce CDK inhibitor resistance by a number of mechanisms[58,59] such as Rb absence or increase of cyclin proteins. However, the small sample size of the DAP-HER -01 study limits the conclusiveness of these findings, necessitating further research to verify the results.

The Safety of Dalpiciclib

The safety profile of dalpiciclib has been extensively studied, and its AEs have been primarily hematological. According to the DAWNA-1 trial, the most common grade 3/4 AEs were hematological toxicities such as neutropenia (84.2%) and leukopenia (62.1%). SAEs occurred in 5.8% of patients treated with dalpiciclib combined with fulvestrant, compared to 6.7% in the placebo group. Grade 3/4 neutropenia often occurred during the first treatment cycle, and the frequency of these severe AEs decreased with prolonged exposure. Common non-hematological AEs included mild liver enzyme abnormalities and QT interval prolongation, with no drug discontinuation events due to QT interval prolongation.

In the DAWNA-2 trial, 90% (271/302) of patients in the dalpiciclib plus aromatase inhibitor group experienced grade 3/4 AEs, with neutropenia (86%) and leukopenia (67%) being the most frequent. SAEs occurred in 12% of patients, and two treatment-related deaths (of unknown cause) were reported.

The DAP-HER-01 study reported that all 41 patients experienced at least one AE during therapy, with diarrhea (97.6%), leukopenia (95.1%), and neutropenia (95.1%) being the most common. No treatment-related deaths occurred.

In the MUKDEN 01 study, all participants experienced at least one AE, with 55 patients experiencing grade 3/4 AEs such as neutropenia (53%), leukopenia (20%), and diarrhea (17%). No patients discontinued therapy due to AEs, and no SAEs or treatment-related deaths were reported.

Overall, the AEs associated with dalpiciclib are primarily hematological, with neutropenia and leukopenia being the most common. Most grade 3/4 AEs required symptomatic treatment with granulocyte colony-stimulating factor, but the frequency and severity of neutropenia events decreased with longer exposure to dalpiciclib.[51] Non-hematological toxicities included gastrointestinal symptoms such as elevated liver transaminase, nausea, and diarrhea, with occasional cardiac toxicity such as prolonged QT interval and decreased ejection fraction. Some patients found relief by suspending medication or reducing the dose.[54,57] A post-hoc analysis of the DAWNA-2 trial showed that dose reduction due to AEs had no significant impact on patients' PFS.[52]

Comparing to abmaciclib,[36–38] dalpiciclib has a lower rate of diarrhea, and it is less visceral toxicity comparing to ribociclib.[40,41,43] So, during dalpiciclib treatment, regular monitoring of blood counts, liver and kidney function, and electrocardiograms are recommended. Patients experiencing diarrhea should maintain detailed management records, including the frequency of defecation and stool characteristics, to guide the appropriate dosage of dalpiciclib.[60]

The Limitations of Dalpiciclib

Firstly, some scholars have raised concerns regarding the AEs and costs associated with dalpiciclib as first-line therapy.[61] They argue that using dalpiciclib as first-line treatment could increase the duration of exposure to the drug, leading to a higher incidence of grade 3/4 neutropenia and increased patient costs. However, the DAWNA-1 and DAWNA-2 studies indicated that the frequency of grade 3/4 AEs tends to decrease with prolonged exposure, and no instances of febrile neutropenia were reported. Moreover, dalpiciclib has been included in China's medical insurance coverage, which helps to alleviate patient costs.[62] Despite previous findings of dalpiciclib have been proved to benefit for HR+/HER2-BC, the data on OS, quality of life, and long-term toxicity from Phase III clinical trials are not yet mature. Consequently, further follow-up is necessary to fully understand the long-term implications of dalpiciclib treatment.[63]

Secondly, because of CDK4/6 inhibitors' mechanisms of action, previous clinical trials mainly focus on HR+/HER2-BC. But an experiment has verified that the combination of CDK4/6 inhibitor (Palbociclib) and PARP inhibitor could improve PARP inhibitor resistance in TNBC by inhibiting HR and increasing DNA damage.[64] And another experiment has demonstrated that with the transcription factor YB-1 phosphorylation, the PARP1 is upregulated, which may induce CDK4/6 inhibitor resistance,[65] so PARP inhibitor could also offset the resistance of CDK4/6 inhibitor. Besides, sitravatinib, a kind of targeting drug for the TAM receptors, is also revealed to be helpful for improving CDK4/6 inhibitor sensibility for TNBC.[66] But so far, the efficacy of dalpiciclib for TNBC is not clear.

Additionally, the resistance of dalpiciclib should be noticed, in terms of palbociclib, ribociclib and abemaciclib, the resistance mechanisms have been explored widely, there are divided to intrinsic and acquired resistance,[58,59] the mechanisms are mainly summarized for the amplification or loss of cell cycle-related genes or proteins[67–73] and the abnormal activation or inactivation of signaling pathways,[74–77] which compete with CDK4/6 inhibitors and result in the targets of CDK4/6 inhibitors absent or low-expression,[78–81] making CDK4/6 inhibitors invalid. To solve the problem of CDK4/6 inhibitor resistance, there are a number of targeting drugs directed at the error spots, different combinations about CDK4/6 inhibitors and targeting drugs thereupon are under explored. And the biomarkers about CDK4/6 inhibitors resistance have been seeking according to various resistant mechanisms,[82] for example, RB deficiency or high p16 expression,[83] by the manners of liquid biopsy and miRNAs could be used for identifying and predicting CDK4/6 inhibitor resistance.[82] However, the biomarkers about dalpiciclib resistance may differ from other CDK4/6 inhibitors.

Conclusions

According to the current consensus on the application of CDK4/6 inhibitors in China,[5] dalpiciclib combined with fulvestrant is recommended for HR+, HER2- metastatic and recurrent breast cancer that has progressed following prior endocrine therapy. Additionally, dalpiciclib combined with aromatase inhibitors is recommended as initial therapy for HR +, HER2- locally ABC or MBC. Studies such as DAP-HER-01 and MUKDEN 01 have explored various combination regimens and treatment timings for HR+/HER2+ breast cancer. While these studies suggest that the combination of dalpiciclib with anti-HER2 targeted drugs like pyrotinib could benefit patients with HER2+ breast cancer, the small sample sizes limit the robustness of the evidence. Consequently, dalpiciclib has not yet been recommended for TPBC patients, and the therapeutic effects of dalpiciclib combined with pyrotinib in HER2+ breast cancer patients still require further exploration.

Moreover, the studies on dalpiciclib have predominantly focused on the Asian population. To date, the NCCN guidelines have not recommended dalpiciclib for breast cancer therapy. Given the variations in breast cancer molecular types and the heterogeneity among different ethnic groups,[84,85] it is essential to expand the sample size and conduct further trials to verify the efficacy of dalpiciclib across diverse populations. And the problem about resistance of dalpiciclip should be brought to attention in the BC patients who quickly progress after accepting dalpiciclib, and biomarkers should be used to identify which population can benefit from dalpiciclib.according to the biomarkers to identify which population can benefit from dalpiciclip. Overall, the efficacy and resistance mechanisms of dalpiciclib in different breast cancer types, and the optimal timing for its use, need to be further studied.

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