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Research Progress on CDK4/6 Inhibitors Combined with Endocrine Therapy for Advanced Breast Cancer

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Abstract: ***The introduction of CDK4/6 inhibitors has revolutionized the treatment paradigm for hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer. These inhibitors, when combined with endocrine therapy, have shown significant improvements in both progression-free survival (PFS) and overall survival (OS). However, the development of resistance presents substantial challenges that limit their long-term effectiveness. This article provides a review of the mechanisms of action, clinical efficacy, and safety of CDK4/6 inhibitors, as well as treatment after disease progression on a CDK4/6 inhibitor, offering valuable references.***

Keywords: Breast cancer, CDK4/6 inhibitors, Endocrine therapy, Efficacy.

1. Introduction

Breast cancer is the most frequently diagnosed cancer among women globally [1]. Endocrine therapy represents the mainstay treatment for hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer, but most patients eventually develop resistance to monotherapy and relapse [2,3]. Therefore, new therapeutic strategies are urgently needed to overcome resistance and improve survival outcomes. Currently, palbociclib, ribociclib, abemaciclib, and dalpiciclib have been approved for clinical treatment of HR+/HER2- advanced breast cancer patients in combination with endocrine agents. CDK4/6 inhibitors combined with endocrine therapy can enhance the response rate and prolong disease control in HR+/HER2- advanced breast cancer patients [4]. Moreover, CDK4/6 inhibitors are oral drugs, making them more tolerable than traditional intravenous chemotherapies. This article reviews research progress on CDK4/6 inhibitors combined with endocrine therapy for advanced breast cancer.

2. Mechanisms of Action of CDK4/6 Inhibitors

The cell cycle is divided into four stages: G1, S, G2, and M phases. Cyclin-dependent kinases 4 (CDK4) and Cyclin-dependent kinases 6 (CDK6) play a key role in the transition from the G1 phase to the S phase of the cell cycle. They phosphorylate the tumor suppressor retinoblastoma protein (RB), resulting in the release of the E2F transcription factor and driving the cell cycle from G1 to S phase. Overactivation of the CDK4/6 pathway leads to uncontrolled cell proliferation, which is an important mechanism in tumorigenesis [5]. CDK4/6 inhibitors induce cell cycle arrest in the G1 phase by inhibiting RB phosphorylation, thereby inhibiting tumor cell proliferation [6]. CDK4/6 inhibitors can also induce senescence by targeting CDK4/6-specific substrates; senescent cells do not re-enter the cell cycle after the removal of inducing signals and are generally unresponsive to other proliferation signals, thereby delaying tumor growth. During cellular senescence, cells produce and release inflammatory molecules, and through specific gene expression and cytokine secretion, activate immune cells or promote paracrine senescence to exert anti-tumor effects [7]. CDK4/6 inhibitors can also exert anti-tumor effects by enhancing anti-tumor immune responses. A study has shown that CDK4/6 inhibitors reduce the expression of the E2F target gene DNMT1 (DNA Methyltransferase 1), leading to hypomethylation, thereby activating the expression of endogenous retrovirus (ERV) elements, increasing intracellular levels of double-stranded RNA, and triggering a 'viral mimicry' response characterized by interferon production and interferon-stimulated gene (ISG) expression, enhancing tumor antigen presentation [8]. Other studies have shown that CDK4/6 inhibitors enhance cytotoxic T cell function and promote tumor cell clearance mediated by cytotoxic T cells [9]. CDK4/6 inhibitors also promote the development of memory phenotypes by inhibiting CDK4/6 in cytotoxic T cells, enhancing the long-term anti-tumor activity of these T cells, and promoting sustained anti-tumor immunity [10].

3. The Research Progress of CDK4/6 Inhibitors in the Treatment of Advanced Breast Cancer

3.1 Palbociclib

Palbociclib is an oral, small-molecule CDK4/6 inhibitor, and it was the first to be FDA-approved for the treatment of advanced breast cancer. PALOMA-2 is a phase III randomized, double-blind clinical trial involving 666 postmenopausal women with ER (+) HER2 (-) advanced breast cancer who had not previously received treatment for advanced disease. Patients were randomized in a 2:1 ratio to receive either the letrozole combined with palbociclib group or the letrozole combined with placebo group. The results showed that the median progression-free survival (PFS) for patients in the letrozole plus palbociclib group was 27.6 months, an increase of 13.1 months compared to the letrozole plus placebo group (14.5 months) (HR=0.563, P<0.0001). The median overall survival（OS）for the letrozole combined with palbociclib group was 53.9 months, an increase of 2.67 months compared to the letrozole combined with placebo

group (51.2 months) (HR=0.96, P=0.34). Compared to the placebo group, the palbociclib group significantly improved progression-free survival; however, the overall survival did not reach statistical significance. Neutropenia was the most common adverse event with the palbociclib and letrozole combination (82.2% vs. 6.3% in the letrozole plus placebo group) [11, 12]. This study confirmed the efficacy and safety of letrozole combined with palbociclib as a first-line treatment for advanced breast cancer.

The PALOMA-3 study is a randomized, double-blind phase III trial recruiting 521 patients to assess the efficacy of fulvestrant combined with palbociclib as a second-line therapy for hormone receptor-positive, HER2-negative metastatic breast cancer. The study showed that the progression-free survival for the palbociclib plus fulvestrant combination was 6.6 months longer than that of the placebo plus fulvestrant combination (mPFS was 11.2 months vs. 4.6 months; HR=0.50; 95% CI: 0.40-0.62, P<0.0001). The median overall survival was 34.8 months for the palbociclib plus fulvestrant group, compared to 28.0 months for the placebo plus fulvestrant group (HR=0.81; 95% CI: 0.65-0.99). The most common grade 3 or 4 adverse event was neutropenia [13]. This study demonstrated the efficacy and safety of palbociclib as a second-line treatment for patients with hormone receptor-positive, HER2-negative metastatic breast cancer.

3.2 Ribociclib

Ribociclib is the second oral CDK4/6 small-molecule inhibitor approved for marketing, primarily used for the treatment of HR+/HER2- advanced breast cancer patients, especially for initial endocrine therapy in premenopausal or perimenopausal women. The MONALEESA-2 study is a randomized, double-blind phase III clinical trial conducted in 668 postmenopausal HR+/HER2- advanced breast cancer patients, aimed at exploring the efficacy and safety of ribociclib as a first-line treatment for advanced breast cancer. The results indicated that the median PFS in the ribociclib combined with letrozole group was 25.3 months, while the placebo combined with letrozole group was 16 months (HR=0.568, $P=9.63\times10^{-8}$), demonstrating a significant extension in patient median progression-free survival (mPFS). The median overall survival (mOS) for the ribociclib plus letrozole group was also significantly improved compared to letrozole monotherapy, at 63.9 months versus 51.4 months (HR=0.76, P=0.008). The most frequently reported all-cause grade 3 or 4 adverse events (≥15% in either group; ribociclib combined with letrozole group vs. placebo combined with letrozole group) were neutropenia (62%) and leukopenia (21.3%). Ribociclib combined with letrozole is a safe and manageable option for first-line treatment of advanced breast cancer, with most adverse events occurring early and effectively managed through patient monitoring and adjustments in ribociclib dosage [14,15]. The study confirmed the efficacy and safety of ribociclib as a first-line treatment for HR+/HER2- advanced breast cancer patients.

The MONALEESA-3 is a phase III randomized trial assessing the effects of ribociclib in combination with fulvestrant versus fulvestrant alone. This trial mainly focused on postmenopausal women with HR+ and HER2- advanced breast cancer, comprising patients who had not previously received treatment for advanced breast cancer or those who had received first-line endocrine therapy, with 726 patients randomly assigned to either the ribociclib combined with fulvestrant group or the placebo combined with fulvestrant group. The ribociclib group demonstrated an increase in mPFS of 7.8 months compared to the placebo group (20.6 months vs. 12.8 months, HR=0.59, 95% CI: 0.49-0.71), with mPFS improved by 14.4 months in patients receiving first-line treatment (33.6 months vs. 19.2 months, HR=0.55, 95% CI: 0.42-0.72), and by 5.5 months in patients receiving second-line treatment (14.6 months vs. 9.1 months, HR=0.57, 95% CI: 0.44-0.74) [16]. The combination of ribociclib and fulvestrant significantly improved OS. The mOS for the ribociclib group was improved by 10.7 months compared to the placebo group (52.2 months vs. 41.5 months, HR=0.754, 95% CI: 0.620-0.916), with an increase of 15.8 months in patients receiving first-line treatment (67.6 months vs. 51.8 months, HR=0.673, 95% CI: 0.504-0.899), and an increase of 6 months in patients receiving second-line treatment (39.7 months vs. 33.7 months, HR=0.801, 95% CI: 0.614-1.046). Neutropenia was the most common grade 3/4 adverse event [17]. This trial confirmed that ribociclib provides benefits in both PFS and OS for patients receiving first-line and second-line treatments, with good safety profiles, making it a new option for second-line therapy.

3.3 Abemaciclib

Abemaciclib is an orally administered, highly selective small-molecule inhibitor of CDK4 and CDK6. The MONARCH-2 is a Phase III randomized, double-blind clinical trial in HR-positive, HER2-negative advanced breast cancer patients, aimed at assessing the efficacy and safety of abemaciclib or placebo combined with fulvestrant in patients who have progressed on endocrine therapy. Compared to the fulvestrant group, the abemaciclib combined with fulvestrant group significantly prolonged patient mPFS and mOS: mPFS was 16.4 months vs 9.3 months (HR=0.553; 95% CI: 0.449-0.681; P<0.001); mOS was 46.7 months vs 37.3 months (HR=0.757; 95% CI: 0.606-0.945; P=0.01). Common hematological AEs of grade 3 or higher in the abemaciclib group included neutropenia (29.9%), anemia (9.1%), and leukopenia (11.1%). Diarrhea was the most common non-hematological AE in the abemaciclib group, with 64 cases (14.5%) of grade 3 adverse events. Most diarrhea cases were effectively managed with loperamide or dose adjustment; instances of treatment discontinuation due to diarrhea were rare [18]. This study confirmed the efficacy and safety of abemaciclib in combination with fulvestrant as a second-line treatment.

The MONARCH-3 is a double-blind, randomized Phase III study evaluating the efficacy of abemaciclib or placebo in combination with a non-steroidal aromatase inhibitor in 493 postmenopausal women with HR+, HER2- advanced breast cancer who had not received systemic treatment at advanced stages. The mPFS for the abemaciclib group was 29.0 months, compared to 14.8 months for the placebo group (HR=0.535, 95% CI: 0.429-0.668, P<0.0001); the mOS for the abemaciclib group was 66.8 months, compared to 53.7 months for the placebo group (HR=0.804, 95% CI: 0.637-1.015, P=0.0664). Abemaciclib extended the median

overall survival of first-line treatment patients by 13.1 months, but this was not statistically significant. The most common grade 3/4 hematological adverse events in the abemaciclib group were neutropenia (27.5%), anemia (9.5%), and leukopenia (10.7%). Diarrhea was the most common non-hematological adverse event in the abemaciclib group (83.5%) [19]. Therefore, abemaciclib is a viable first-line treatment option for HR+ and HER2- advanced breast cancer patients.

3.4 Dalpiciclib

Dalpiciclib is a Chinese-origin CDK4/6 inhibitor approved by China National Medical Products Administration (NMPA) for first-line and second-line treatment of HR+/HER2- advanced breast cancer. DAWNA-2 is a randomized, double-blind, placebo-controlled Phase III clinical trial that investigated the efficacy and safety of dalpiciclib in combination with letrozole or anastrozole as first-line treatment for hormone receptor-positive, HER2-negative advanced breast cancer, enrolling a total of 580 patients. The results indicated that dalpiciclib combined with endocrine therapy significantly extended patients' PFS compared to the placebo group (30.6 months vs 18.2 months, HR=0.51, 95% CI: 0.38–0.69, P<0.0001). The most frequently reported serious adverse events were neutropenia and leukopenia [20]. This study confirmed the efficacy and safety of dalpiciclib in combination with endocrine therapy as a first-line treatment.

The DAWNA-1 trial is a randomized, double-blind Phase III clinical trial investigating the efficacy and safety of dalpiciclib combined with fulvestrant as second-line treatment for hormone receptor-positive, HER2-negative advanced breast cancer. The results indicated that, compared to the placebo plus fulvestrant group, the dalpiciclib plus fulvestrant group significantly improved the primary endpoint of progression-free survival. The PFS for the dalpiciclib plus fulvestrant group was 15.7 months, while the placebo group had 7.2 months (HR=0.42, 95% CI=0.31–0.58; P<0.0001). The most common grade 3 or 4 adverse events were hematological, including neutropenia (84.2%), leukopenia (62.1%), thrombocytopenia (5.8%), and lymphocytopenia (4.2%), with safety being manageable [21]. Dalpiciclib as a second-line treatment for HR+HER2- advanced breast cancer shows significant improvement in PFS and safety; however, whether there is an overall survival benefit remains to be evaluated with continued follow-up.

4. Treatment after Disease Progression on a CDK4/6 Inhibitor

CDK4/6 inhibitors are an important therapy for HR+/HER2- advanced breast cancer, significantly improving patients' PFS and OS. However, resistance inevitably develops during treatment, impacting its efficacy. Therefore, studying treatment strategies after resistance to a CDK4/6 inhibitor is of great importance for further improving patient prognosis.

CDK4/6 inhibitors are frequently combined with fulvestrant or aromatase inhibitor (AI), and when patients experience progression after CDK4/6 inhibitor treatment, it is common in clinical practice to switch to a different endocrine therapy combined with another CDK4/6 inhibitor. The MAINTAIN trial is a phase II, randomized, double-blind, placebo-controlled study aimed at comparing the efficacy of switching endocrine therapy combined with ribociclib to switching endocrine therapy combined with placebo in patients whose tumors progressed after treatment with CDK4/6 inhibitors and endocrine therapy. Among the 119 patients randomly assigned, 103 (86.5%) had previously received palbociclib, and 14 participants received ribociclib (11.7%). Compared to the group switching to endocrine therapy combined with placebo, patients in the ribociclib combination group showed a significant improvement in mPFS (5.29 months vs. 2.76 months, HR=0.57, 95% CI: 0.39-0.85, P=0.006) [22]. This trial demonstrated the efficacy of switching endocrine therapy combined with another CDK4/6 inhibitor as a treatment option after CDK4/6 inhibitors, but further large-scale randomized controlled trials are needed for additional validation.

Switching endocrine therapy after progression on CDK4/6 inhibitors combined with endocrine treatment is also a treatment option. The PADA-1 trial is a phase III, open-label study that randomly assigned 172 patients with elevated bESR1mut levels to treatment groups, with 88 patients receiving a switch to fulvestrant and palbociclib, while 84 patients continued with AI and palbociclib. The study indicated that for HR+/HER2- advanced breast cancer patients who experienced elevated bESR1mut levels after first-line treatment with palbociclib combined with AI, switching to fulvestrant combined with palbociclib extended the patients' mPFS compared to continuing with AI and palbociclib (11.9 months vs. 5.7 months, HR=0.61, 95% CI: 0.43-0.86; P=0.0040) [23]. Elacestrant is a new non-steroidal oral selective estrogen receptor degrader (SERD) that degrades ER and inhibits ER-mediated gene transcription and tumor growth dependent on estradiol [24]. The EMERALD trial is a multicenter, randomized, open-label phase III clinical trial that randomly assigned 477 patients with ER-positive, HER2-negative advanced breast cancer, who had previously received 1-2 lines of endocrine therapy combined with CDK4/6 inhibitors, to either the Elacestrant group or the endocrine monotherapy group, with the latter selecting a different endocrine treatment from what the patients had previously received, such as fulvestrant, anastrozole, letrozole, or exemestane. The trial results showed a statistically significant extension in PFS for the Elacestrant group compared to the endocrine monotherapy group (HR = 0.70; 95% CI: 0.55 -0.88; P =0.002), with 12-month PFS rates of 22.3% and 9.4%, respectively. In patients with ESR mutations, the Elacestrant group also exhibited extended PFS (HR = 0.55; 95% CI: 0.39-0.77; P =0.0005), with 12-month PFS rates of 26.8% and 8.2%. The most common grade 3/4 adverse events were nausea (2.5%), back pain (2.5%), and elevated ALT (2.1%). Elacestrant demonstrated a significant improvement in PFS compared to endocrine monotherapy in second-line or third-line treatment of ER-positive, HER2-negative advanced breast cancer patients, with manageable safety [25].

More targeted drugs are now being used to treat patients with breast cancer who have developed resistance to endocrine therapy. Activation of the PI3K/AKT/mTOR signaling pathway is a key mechanism contributing to resistance in HR+/HER2- advanced breast cancer patients. Capivasertib is an AKT inhibitor that has shown synergistic antitumor

activity when combined with endocrine therapy in preclinical models. The CAPItello-291 trial is a phase III study that evaluated the efficacy and safety of capivasertib combined with fulvestrant in hormone receptor-positive, HER2-negative advanced breast cancer patients with disease progression during or after AI treatment. A total of 708 patients were randomly assigned to either the capivasertib plus fulvestrant group or the placebo plus fulvestrant group, with 489 (69.1%) having previously received CDK4/6 inhibitor treatment for advanced breast cancer. The study demonstrated that the mPFS in the capivasertib plus fulvestrant group was 7.2 months, compared to 3.6 months in the placebo plus fulvestrant group (HR=0.60, 95% CI: 0.51-0.71, P<0.001). Among patients receiving capivasertib combined with fulvestrant, the most common grade 3 or higher adverse events were rash (12.1%) and diarrhea (9.3%) [26]. Capivasertib combined with fulvestrant can significantly enhance PFS in patients who progressed during treatment with aromatase inhibitors, whether or not combined with CDK4/6 inhibitors, and shows favorable safety. Alpelisib is a PI3K inhibitor, and the SOLAR-1 study demonstrated that in patients with HR+HER2− advanced breast cancer and PIK3CA mutations, alpelisib combined with fulvestrant extended PFS by 5.3 months compared to placebo plus fulvestrant (11 months vs. 5.7 months; HR=0.65, 95% CI: 0.50-0.85, P<0.001), although only 5.9% of patients had previously received CDK4/6 inhibitor treatment [27]. The phase II BYLieve trial showed that alpelisib combined with endocrine therapy provided a mOS of 26.4 months and a mPFS of 7.3 months in HR (+) HER2 (-) advanced breast cancer patients with PIK3CA mutations who progressed during or after treatment with CDK4/6 inhibitors [28]. Therefore, for PIK3CA-mutated patients who progress during or after CDK4/6 inhibitor treatment, alpelisib combined with endocrine therapy is also a treatment option in subsequent lines. Everolimus is an oral mTOR inhibitor recommended by the CSCO guidelines for use in patients who have failed treatment with CDK4/6 inhibitors. The TRINITI-1 trial is an open-label, single-arm, phase I/II clinical study aimed at exploring the efficacy of ribociclib plus everolimus and exemestane in HR+/HER2- advanced breast cancer patients who progressed after previous treatment with CDK4/6 inhibitors. Results showed a clinical benefit rate of 41.1% at 24 weeks, with a median PFS of 5.7 months in the evaluable population, indicating a certain degree of clinical benefit [29]. Therefore, mTOR inhibitors are a good option for patients who have failed CDK4/6 treatment. Tucidinostat is an oral subtype-selective histone deacetylase (HDAC) inhibitor. The ACE study is a randomized, double-blind, placebo-controlled phase III clinical trial that included 365 patients with HR-positive, HER2-negative advanced breast cancer who relapsed or progressed after at least one endocrine therapy. The study showed that tucidinostat combined with exemestane demonstrated improved progression-free survival compared to placebo combined with exemestane (7.4 months vs. 3.8 months; HR=0.75, 95% CI: 0.58-0.98; p=0.033) [30]. Therefore, tucidinostat may be considered as a treatment option in subsequent lines for patients who have failed CDK4/6 inhibitor combined endocrine therapy.

Chemotherapy is one of the treatment options for HR+/HER2− advanced breast cancer and is often an important choice after progression on CDK4/6 inhibitors. A real-world study from Russia enrolled 54 patients with HR+ HER2− advanced breast cancer, all of whom received at least one line of treatment with abemaciclib after CDK4/6 inhibitor therapy. The results showed an objective response rate of 24%, a disease stabilization rate of 67%, a progression rate of 9%, and a median progression-free survival of 10.0 months [31].

5. Summary

The combination of CDK4/6 inhibitors and endocrine therapy can prolong patients' PFS and OS. However, overcoming resistance remains a top priority for future research. The continued exploration of combination strategies, novel agents, and the integration of precision medicine approaches will be pivotal in maximizing the potential of CDK4/6 inhibitors and achieving durable responses for patients with advanced breast cancer.

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