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Resistance mechanisms and coping strategies of CDK4/6 inhibitors in treatment of breast cancer

CHEN Guo*, HU Dandan, ZHANG Xiaoqing

**The First Clinical College, Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210023, China*

Corresponding author: ZHANG Xiaoqing, E-mail: zxqing1983@163.com

Abstract: The standard first-line treatment for advanced hormone receptor-positive（HR+）, human epidermal growth factor receptor 2 negative (HER2-) breast cancer is the combination of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors and endocrine therapy, which significantly prolongs patients progression-free survival. However, clinical resistance to CDK4/6 inhibitors severely impacts patients prognosis. The resistance mechanisms of CDK4/6 inhibitors are complex, involving multiple dimensions such as abnormal cell cycle regulation, activation of growth factor receptors and signaling pathways, abnormal immune regulation, and autophagy activation. Current strategies to address resistance include diverse approaches: combination with other endocrine agents［selective estrogen receptor degraders（SERDs）and selective estrogen receptor covalent antagonists（SERCAs）］, continuation use of CDK4/6 inhibitors （cross-line therapy and new-generation inhibitors), switching to alternative targeted therapies［PI3K/AKT/mTOR pathway inhibitors, antibody-drug conjugate（ADC）, poly ADP-ribose polymerase (PARP) inhibitors, histone deacetylase (HDAC) inhibitors] and chemotherapy. Clinical practice requires tailoring precision treatment strategies based on individual patient characteristics. This article systematically reviews the research progress on the resistance mechanisms of CDK4/6 inhibitors in breast cancer and corresponding therapeutic strategies.

Keywords: Cyclin-dependent kinase 4/6 inhibitor; Breast cancer; Drug resistance; Human epidermal growth factor receptor 2; Treatment strategy

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Breast cancer ranks first among female malignant tumors worldwide, and hormone receptor (HR)+/human epidermal growth factor receptor 2 (HER2)- breast cancer accounts for approximately 70% of all breast cancer cases [1]. At present, patients with HR+ breast cancer require 5-10 years of endocrine therapy, and 20%-40% of patients experience recurrence and metastasis due to drug resistance [2]. Endocrine therapy remains the first-line treatment for patients with HR+/HER2- breast cancer accompanied by asymptomatic visceral metastasis. Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors suppress the proliferation of tumor cells by regulating cell cycle progression. Currently, the *5th ESO-ESMO international consensus guidelines for advanced breast cancer（ABC5）* [3] and the *Breast cancer, version 3.2024, NCCN clinical practice guidelines in oncology* [4] recommend CDK4/6 inhibitor combined with endocrine therapy as the standard treatment for progressive HR+/HER2- breast cancer. Regimens combining CDK4/6 inhibitors with third-generation aromatase inhibitors or fulvestrant, a selective estrogen receptor degrader (SERD), serve as the standard first- and second-line therapeutic options for advanced HR+/HER2- breast cancer, which can significantly prolong patients' progression-free survival (PFS). Four types of CDK4/6 inhibitors have been approved for marketing by the National Medical Products Administration in China, namely palbociclib, ribociclib, abemaciclib and dalpiciclib, all of which have demonstrated favorable clinical efficacy in combination with endocrine agents [5].

Nevertheless, the median PFS is approximately 2 years following first-line treatment with CDK4/6 inhibitors combined with aromatase inhibitors in advanced settings [6]. It is evident that drug resistance severely limits therapeutic efficacy, drives disease progression, and adversely affects patients' long-term prognosis. Therefore, in-depth exploration of therapeutic strategies after CDK4/6 inhibitor resistance is of great clinical significance.

1 Mechanisms of CDK4/6 Inhibitor Resistance

Aberrant overexpression of *WEE*1 and *MDM*2 genes, activation of histone deacetylase (HDAC), amplification of CDK2/4/6 and cyclin E1, as well as functional loss of Rb, FZR1 and FAT atypical cadherin 1 proteins, may lead to dysregulated cell cycle progression, reduce the sensitivity of tumor cells to CDK4/6 inhibitors, and ultimately induce drug resistance [7-8]. Activation of growth factor receptors and downstream signaling pathways, such as fibroblast growth factor receptor (FGFR) 1 and the PI3K/AKT/mTOR axis, can facilitate tumor cell proliferation and trigger the development of drug resistance. Accumulating evidence has confirmed

that resistance to CDK4/6 inhibitors in tumor cells can be reversed by inhibiting aberrant FGFR activity [9].

Meanwhile, relevant studies have demonstrated that in palbociclib-resistant cell lines, the mutation frequency of key immune regulatory genes related to T cell activation and cytotoxicity is markedly increased. Mutations in these immune-related genes disrupt CDK4/6 inhibitor-mediated immune pathway homeostasis [10], impair the function of immune cells and the expression of immune molecules in the tumor microenvironment, induce tumor immune escape, and consequently result in drug resistance.

In addition, autophagy activation not only reverses CDK4/6 inhibitor-induced cell cycle arrest but also participates in the development of CDK4/6 inhibitor resistance [11], exerting dual regulatory effects in breast cancer cells.

2 Therapeutic Strategies After CDK4/6 Inhibitor Resistance

2.1 Combination with Alternative Endocrine Agents

2.1.1 Selective Estrogen Receptor Degraders (SERDs)

SERDs specifically degrade estrogen receptors, thereby blocking estrogen signaling cascades and suppressing tumor growth. Fulvestrant, a selective estrogen receptor downregulator, can completely block estrogen receptors and the transduction of downstream signaling pathways. In the overall population of patients with HR+/HER2- advanced breast cancer, the median PFS of fulvestrant monotherapy was 8.5 months (95%*CI*: 7.0-10.0 months) [12]. Compared with placebo combined with fulvestrant, the combination of CDK4/6 inhibitors and fulvestrant significantly prolonged PFS (*HR*=0.51, *P*<0.05) and overall survival (OS) (*HR*=0.73, *P*<0.05) in breast cancer patients with endocrine resistance.
Although this combination regimen may induce hematological adverse reactions, all adverse events are clinically manageable and tolerable [13].

Next-generation oral SERDs, such as elacestrant and giredestrant, have exhibited superior efficacy to fulvestrant in clinical trials and can notably extend the median PFS in patients with estrogen receptor mutations (*HR*=0.55, *P*<0.05) [14]. However, clinical studies investigating the combination of CDK4/6 inhibitors and elacestrant remain absent to date. The *Guidelines for breast cancer diagnosis and treatment by China Anti-cancer Association(2024 edition)* recommend elacestrant for the treatment of *ESR*1-mutant HR+/HER2- advanced breast cancer [15].

2.1.2 Selective Estrogen Receptor Covalent Antagonists (SERCA)

The core mechanism of endocrine resistance in breast cancer is ESR1 mutation-mediated ligand-independent activation, which weakens drug binding affinity. As a novel SERCA, H3B-6545 irreversibly binds covalently to cysteine residues of ERα, thereby restoring tumor cell sensitivity to endocrine agents [16].

Johnston *et al.* [17] administered H3B-6545 in combination with palbociclib to patients with CDK4/6 inhibitor resistance, with a median PFS of 11.5 months and a 12-month overall survival rate of 72.5% (95%CI: 50.1%-86.1%). Hamilton *et al.* [18] evaluated the efficacy of single-agent H3B-6545, reporting a median PFS of 5.06 months and a median OS of 21.52 months. The above studies have verified that H3B-6545 at the recommended dose exerts potent preliminary anti-tumor activity. Nevertheless, H3B-6545 is currently in phase II clinical trials, and additional clinical evidence is required to validate its clinical efficacy and safety profile.

2.2 Continued Application of CDK4/6 Inhibitors

2.2.1 Cross-line Therapy with Approved CDK4/6 Inhibitors

The PALOMA-3 [19], MONARCH 2 [20], and MONALEESA-3 [21] trials adopted palbociclib, abemaciclib and ribociclib combined with fulvestrant as second-line regimens for HR+/HER2- advanced breast cancer, respectively, achieving significant improvements in median PFS of 11.2 months, 16.4 months and 20.5 months. With regard to second-line treatment options for patients with first-line CDK4/6 inhibitor resistance, the PACE trial yielded negative outcomes for cross-line treatment with palbociclib [22]. The MAINTAIN and TRINITI-1 studies confirmed that sequential treatment with ribociclib significantly prolonged median PFS [23-24]. In 2024, updated data from the postMONARCH trial presented at the American Society of Clinical Oncology (ASCO) annual meeting demonstrated that the 6-month progression-free survival rate was 50% in the abemaciclib group versus 37% in the placebo group. Abemaciclib combined with fulvestrant significantly improved PFS in eligible patients (*P*=0.01) [25]. Patients previously treated with palbociclib derived the most prominent survival benefit from subsequent abemaciclib therapy (*HR*=0.62), confirming that switching to an alternative CDK4/6 inhibitor after disease progression on prior CDK4/6 inhibitor treatment is a viable therapeutic strategy [25]. Notably, only 8% of participants in this trial had prior exposure to abemaciclib, with a limited sample size. Thus, current evidence cannot confirm whether re-administration of the same CDK4/6 inhibitor confers clinical benefits in drug-resistant populations. A pooled analysis of 18 clinical studies conducted by Ravani *et al.* [26] indicated that continued CDK4/6 inhibitor treatment in later lines was correlated with prolonged PFS (*HR*=0.64, *P*<0.01) and OS (*HR*=0.70, *P*<0.01). Furthermore, both maintenance of the original CDK4/6 inhibitor (*HR*=0.62, *P*<0.01) and switching to a different CDK4/6 inhibitor (*HR*=0.49, *P*<0.01) provided significant PFS benefits.

Collectively, these findings suggest that cross-line CDK4/6 inhibitor therapy is a reasonable and effective option for patients without actionable target mutations or

ineligible for alternative targeted agents. Given the high heterogeneity among patients with CDK4/6 inhibitor resistance, the efficacy of CDK4/6 inhibitors is influenced by multiple factors including patient characteristics and combination regimens. Treatment selection should be individualized and precisely tailored based on clinical conditions.

2.2.2 Novel CDK4/6 Inhibitors and Selective CDK4 Inhibitors

Lerociclib (GB491), a next-generation potent and highly selective oral CDK4/6 inhibitor, exhibits high activity against CDK4/cyclin D1 and CDK6/cyclin D3, as well as moderate inhibitory activity on CDK9/cyclin T in preclinical studies. The phase III LEONARDA-1 trial demonstrated that lerociclib combined with fulvestrant prolonged median PFS to 11.07 months (P<0.01) with a superior safety profile compared with conventional CDK4/6 inhibitors [27].

PF-07220060, a novel selective CDK4 inhibitor, was reported at the 2024 European Society for Medical Oncology (ESMO) Breast Cancer Congress. In HR+/HER2- metastatic breast cancer patients previously treated with CDK4/6 inhibitors and endocrine therapy, combination treatment with PF-07220060 plus letrozole or fulvestrant achieved a median PFS of 8.1 months with a low incidence of hematological toxicities and favorable safety, representing a promising novel therapeutic option for CDK4/6 inhibitor-pretreated patients [28].

2.3 Switch to Alternative Targeted Therapy

2.3.1 Targeted Therapy Against the PI3K/AKT/mTOR Pathway

The PI3K/AKT/mTOR signaling axis regulates tumor cell growth and proliferation, with gene mutations in this pathway detected in approximately 50% of advanced breast cancer patients [29]. The PI3K/AKT/mTOR pathway plays a pivotal role in breast cancer tumorigenesis and progression and is closely implicated in the emergence of CDK4/6 inhibitor resistance [30-31]. Combination regimens targeting this pathway with CDK4/6 inhibitors have shown favorable efficacy in clinical investigations.

Pathway-specific inhibitors are classified into three categories: PI3K inhibitors (e.g., taselisib, alpelisib), AKT inhibitors (e.g., capivasertib), and mTOR inhibitors (e.g., everolimus).

Everolimus, a classic mTOR inhibitor, yielded significant PFS improvement in the phase III BOLERO-2 trial, with a median PFS of 6.9 months in the everolimus plus exemestane group versus 2.8 months in the control group (P<0.01) [32]. Although the everolimus group presented higher toxicity than the placebo group, the combination of everolimus and exemestane remains a viable therapeutic option for CDK4/6 inhibitor-resistant breast cancer after balancing clinical benefits and adverse reactions. The BOLERO-5 trial further validated the clinical benefits of everolimus combined with exemestane in postmenopausal Chinese women with breast cancer. This combination regimen significantly prolonged PFS with a favorable safety profile in the Chinese population, and most adverse events were mild to moderate and manageable via dose adjustment and symptomatic intervention [33].

Inavolisib, a novel next-generation PI3K inhibitor [34], has demonstrated robust anti-tumor efficacy in interim analyses of the INAVO120 trial [35]. This trial enrolled HR+/HER2- patients with endocrine resistance and *PIK3CA* mutations, who received triple therapy with inavolisib, palbociclib and fulvestrant. The median PFS was 7.3 months in the placebo group and 15.0 months in the inavolisib group in initial reports. Updated data released at the 2024 ASCO annual meeting showed that the median PFS was extended to 24.0 months in the inavolisib group versus 15.1 months in the control group [35]. In October 2024, the US Food and Drug Administration (FDA) approved the combination of inavolisib, palbociclib and fulvestrant for HR+/HER2- breast cancer patients with PIK3CA mutations and resistance to adjuvant endocrine therapy.

The *Guidelines of CHINESE Society of Clinical Oncology (CSCO) Breast Cancer* [36] recommends AKT inhibitor combined with endocrine therapy as a grade III option for patients with disease progression after CDK4/6 inhibitor treatment. The CAPItello-291 trial investigated capivasertib plus fulvestrant in patients with aberrant PI3K/AKT1/PTEN signaling pathways, among whom 69.1% had prior CDK4/6 inhibitor exposure. This regimen significantly prolonged PFS in patients with HR+/HER2- advanced breast cancer with a well-tolerated safety profile [37]. These clinical findings provide high-level evidence to support this regimen as a preferred salvage treatment for HR+/HER2- advanced breast cancer following CDK4/6 inhibitor failure.

2.3.2 Antibody–Drug Conjugates (ADCs)

Antibody–drug conjugates consist of three core components: monoclonal antibodies, linkers and cytotoxic payloads, which specifically deliver chemotherapeutic agents to tumor cells and exert precise anti-tumor cytotoxicity [38].

Currently, novel ADC agents widely applied in breast cancer treatment include trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan. Trophoblast cell-surface antigen 2 (Trop-2), a transmembrane calcium signaling transducer, has emerged as a novel and promising molecular target for tumor targeted therapy [39]. Sacituzumab govitecan, a Trop-2-targeted ADC, achieved favorable efficacy and safety in the TROPiCS-02 trial, with a median PFS of 5.5 months and a median OS of 14.4 months [40]. For HR+/HER2- advanced breast cancer patients with CDK4/6 inhibitor failure, sacituzumab govitecan confers superior PFS and OS benefits compared with conventional single-agent chemotherapy [15]. The DESTINY-Breast06 trial confirmed that T-DXd provided significant PFS improvement over standard chemotherapy in CDK4/6 inhibitor-resistant patients (13.2 months vs 8.1 months) [41]. Dawood et al. [42] found that in patients with

advanced breast cancer previously treated with CDK4/6 inhibitors combined with endocrine therapy, both T-DXd and sacituzumab govitecan could significantly improve the 5-year overall survival rate (T-DXd: 74.8% versus 52.2%, $P<0.05$; sacituzumab govitecan: 73.4% versus 64.7%, $P<0.05$). The 2024 ESMO Clinical Practice Guidelines recommend T-DXd for HER2-low-expressing patients and sacituzumab govitecan for HER2- patients with rapid disease progression after first-line CDK4/6 inhibitor combined endocrine therapy.

Datopotamab deruxtecan is another novel Trop-2-targeted ADC that selectively delivers cytotoxic agents to tumor cells and reduces off-target systemic toxicity. The phase III TROPION-Breast01 trial revealed that datopotamab deruxtecan significantly prolonged median PFS compared with conventional regimens in HR+/HER2- advanced breast cancer patients with endocrine resistance (6.9 months vs 4.9 months, $P<0.05$) [43]. Updated patient-reported outcomes presented at the 2024 ESMO Breast Cancer Congress indicated that datopotamab deruxtecan significantly delayed the deterioration of secondary endpoints including global health status, quality of life, physical function and pain control [44]. Compared with traditional therapeutic strategies, datopotamab deruxtecan delivers enhanced anti-tumor efficacy with manageable safety profiles and improves long-term quality of life, serving as a well-tolerated novel treatment option.

However, Trop-2-targeted ADCs have not yet been approved for clinical use in mainland China, and additional clinical trials are required to verify their domestic efficacy and safety.

2.3.3 Poly (ADP-Ribose) Polymerase (PARP) Inhibitors

DNA damage mainly includes DNA single-strand breaks (SSBs) and DNA double-strand breaks (DSBs). Among the 18 identified PARP isoforms, only PARP1 and PARP2 are responsible for physiological DNA damage repair. Deficient PARP activity leads to impaired or inaccurate DNA repair, resulting in chromosomal mutation and aberration. PARP inhibitors suppress the catalytic function of PARP, interfere with the repair of DNA single-strand breaks, block tumor cell DNA replication, and ultimately exert anti-cancer effects.

Breast cancer susceptibility gene 1/2 (*BRCA*1/2) are critical tumor suppressor genes that maintain genomic stability via homologous recombination-mediated DNA double-strand break repair. Pathogenic *BRCA*1/2 mutations induce genomic instability and increase the risk of multiple malignancies including breast and ovarian cancer. *BRCA*2 mutations are predominantly detected in *HR*+ breast cancer and associated with a high recurrence risk [45]. Patients with germline *BRCA*-mutant breast cancer exhibit poor survival outcomes and elevated mortality risk, highlighting the necessity of genetic screening for high-risk populations in early clinical stages.

Tumor cells retain proliferative capacity with the deficiency of either *PARP* or *BRCA*1/2. In *BRCA*1/2-deficient tumor cells, PARP inhibitor monotherapy blocks single-strand break repair, and the dual impairment of single- and double-strand DNA repair pathways triggers irreversible tumor cell apoptosis [46], which constitutes the core therapeutic mechanism of PARP inhibitors in *BRCA*-mutant malignancies. PARP inhibitors promote error-prone non-homologous end joining, increase DNA repair error rates, and inhibit continuous tumor cell proliferation [47]. Accordingly, genetic testing for *BRCA*1/2 mutations is strongly recommended for HR+/HER2- breast cancer patients with endocrine resistance who have not undergone hereditary susceptibility gene detection. PARP inhibitors should be prioritized for patients harboring pathogenic BRCA mutations.

Olaparib is the most representative commercially available PARP inhibitor. The FDA and European Medicines Agency approved olaparib in January 2018 and March 2019, respectively, for the treatment of locally advanced or metastatic gBRCAm/HER2- breast cancer. In March 2022, the FDA further expanded its indication to high-risk early-stage gBRCAm/HER2- breast cancer patients after neoadjuvant or adjuvant chemotherapy, enabling precise early and late-stage intervention for BRCA-mutant breast cancer.

In the phase III clinical trial of olaparib for *BRCA*-mutant HER2- metastatic breast cancer, olaparib monotherapy prolonged median PFS by 2.8 months and reduced the risk of disease progression or death by 42% compared with standard single-agent chemotherapy ($P<0.05$) [48], with a median OS of 19.3 months ($P<0.05$) [49], confirming the superior efficacy of olaparib over conventional chemotherapy.

Guidelines for breast cancer diagnosis and treatment by China Anti-cancer Association (2024 edition) [15] recommend PARP inhibitors such as olaparib as alternative options for advanced breast cancer patients with germline *BRCA*1/2 mutations. Nevertheless, these agents have not been officially approved for breast cancer indications in China.

2.3.4 HDAC Inhibitors

Preclinical studies have demonstrated that HDAC inhibitors suppress the transcription of estrogen receptors and downstream responsive genes in HR+ breast cancer cells. In HR- breast cancer cells, HDAC inhibitors upregulate estrogen receptor expression, indicating their dual role in enhancing and restoring the anti-tumor effects of endocrine therapy [50]. Multiple clinical trials have validated that HDAC inhibitors can reverse endocrine resistance when combined with endocrine agents in HR+ breast cancer [51].

Tucidinostat, a benzamide-class selective HDAC subtype inhibitor, is the first domestically developed HDAC inhibitor approved in China. A real-world clinical study showed that among HR+/HER2- metastatic breast cancer patients with disease progression after CDK4/6 inhibitor treatment, the median PFS was 4.5 months in patients receiving immediate tucidinostat treatment, while the overall median PFS of the entire cohort was only 2.0

months [51]. In 2019, tucidinostat combined with aromatase inhibitors was approved for postmenopausal HR+/HER2- locally advanced or metastatic breast cancer patients with recurrence or progression after prior endocrine therapy. Consistently, the CSCO guidelines recommend tucidinostat plus exemestane as a standard salvage regimen for *HR*+ breast cancer patients with failure to tamoxifen and/or non-steroidal aromatase inhibitors.

Entinostat is the first HDAC inhibitor with confirmed anti-tumor efficacy in phase II breast cancer trials. Yardley *et al.* [52] reported that entinostat combined with exemestane yielded superior efficacy to exemestane monotherapy in 130 HR+/HER2- metastatic breast cancer patients with aromatase inhibitor resistance, with a 2-month PFS extension and an 8.3-month OS extension. However, the phase III CONNECT trial conducted by Connolly *et al.* [53] enrolled 608 eligible patients and revealed comparable efficacy between entinostat plus exemestane and exemestane monotherapy (PFS: 3.3 months vs 3.1 months; OS: 23.4 months vs 21.7 months). Thus, the survival benefit of adding entinostat to endocrine regimens for aromatase inhibitor-resistant HR+/HER2- breast cancer remains controversial.

A nationwide phase III clinical trial conducted in China was performed to evaluate the efficacy and safety of entinostat in Chinese breast cancer populations. The results demonstrated that the median PFS was significantly prolonged in the entinostat plus exemestane group compared with the placebo group (6.32 months vs 3.72 months), with a 24% reduction in the risk of disease progression or death (*HR*=0.76, *P*=0.046). The median OS was 38.55 months in the entinostat group, representing an over 9-month OS extension and a 25% reduction in mortality risk (*HR*=0.75). Significant clinical benefits were also observed in patients with CDK4/6 inhibitor resistance and prior chemotherapy exposure. Moreover, patients without visceral metastasis, primary endocrine resistance and no prior fulvestrant treatment derived more prominent therapeutic benefits from entinostat combination therapy.

On April 30, 2024, the National Medical Products Administration officially approved the indication of entinostat tablets: combined with aromatase inhibitors for the treatment of *HR*+, HER2- locally advanced or metastatic breast cancer with recurrence or progression after prior endocrine therapy.

2.4 Conversion to Chemotherapy

Due to inherent differences in drug sensitivity, HR+/HER2- breast cancer exhibits a significantly lower pathological complete response (pCR) rate after neoadjuvant chemotherapy compared with other molecular subtypes [55]. Nevertheless, a high Ki-67 proliferation index indicates an increased proportion of proliferating tumor cells and is correlated with enhanced chemotherapy sensitivity in HR+/HER2- breast cancer [56]. Furthermore, chemotherapy is indicated for patients with endocrine resistance and symptomatic visceral metastasis, aiming to alleviate clinical symptoms, improve quality of life and prolong long-term survival. Therefore, conventional chemotherapy remains an indispensable component of salvage treatment for CDK4/6 inhibitor-resistant breast cancer. Common chemotherapy regimens include anthracyclines, taxanes, capecitabine and platinum-based agents, which can be administered as monotherapy or combination regimens. While chemotherapy effectively controls tumor progression and relieves systemic symptoms, it is accompanied by inevitable adverse reactions such as myelosuppression and gastrointestinal toxicity. Close monitoring of treatment-related adverse events and comprehensive supportive interventions, including probiotic supplementation, moxibustion combined with acupoint application, and acupuncture therapy, are essential during chemotherapy.

Kim *et al.* [57] enrolled premenopausal patients with locally advanced HR+/HER2- breast cancer and found that neoadjuvant chemotherapy combined with ovarian function suppression significantly improved the pCR rate and reduced Ki-67 expression compared with chemotherapy alone. Clinical evidence has verified that neoadjuvant chemotherapy plus ovarian function suppression remarkably improves disease-free survival in young HR+/HER2- breast cancer patients aged ≤35 years [58]. Hence, the addition of ovarian function suppression to neoadjuvant chemotherapy is recommended for young patients with locally advanced HR+/HER2- breast cancer.

3 Discussion

Substantial advances have been achieved in the comprehensive management of HR+ breast cancer in recent decades. In particular, the wide application of CDK4/6 inhibitor combined endocrine therapy has dramatically improved PFS and OS in advanced breast cancer patients. However, the emergence of CDK4/6 inhibitor resistance poses a major clinical challenge for long-term disease control. Fortunately, a variety of optimized salvage therapeutic strategies have been developed to address this clinical dilemma.

For the majority of eligible patients, cross-line sequential treatment with CDK4/6 inhibitors combined with endocrine agents achieves durable PFS benefits. In parallel, continuous research and structural optimization of next-generation CDK4/6 inhibitors and novel selective CDK4 inhibitors aim to overcome intrinsic and acquired drug resistance, showing promising clinical application prospects. Rational combination of endocrine agents targeting different nodes of hormone receptor signaling pathways, sequential targeted therapy and combination chemotherapy exert synergistic anti-tumor effects and further enhance therapeutic efficacy. Despite high inter-individual tumor heterogeneity, clinicians can formulate personalized combination regimens based on comprehensive clinical evaluation. Precision individualized treatment maximizes anti-tumor efficacy, minimizes treatment-related adverse reactions, prolongs overall survival and relieves cancer-related symptoms.

In summary, multiple diversified therapeutic options with distinct advantages are currently available for patients with CDK4/6 inhibitor-resistant HR+/HER2- breast cancer, providing abundant clinical choices for individualized salvage treatment.

Conflict of Interest: None

Reference

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·乳腺癌专题·研究进展·

CDK4/6抑制剂在乳腺癌治疗中的耐药机制及应对策略

陈果[1]， 胡丹丹[1]， 张晓清[2]

1. 南京中医药大学第一临床医学院，江苏 南京 210023；2. 南京中医药大学附属医院乳腺外科，江苏 南京 210029

摘要：激素受体阳性(HR+)、人类表皮生长因子受体2阴性(HER2-)晚期乳腺癌一线标准治疗方案为细胞周期蛋白依赖性激酶4/6(CDK4/6)抑制剂联合内分泌治疗，可显著延长患者无进展生存期，但CDK4/6抑制剂的临床耐药性严重影响患者预后。CDK4/6抑制剂耐药机制复杂，涉及细胞周期调控异常、生长因子受体及信号通路激活、免疫调控异常及自噬激活等多方面。当前，针对耐药的治疗策略多样，包括联合其他内分泌药物[选择性雌激素受体降解剂(SERDs)、雌激素受体共价拮抗剂(SERCAs)]、继续使用CDK4/6抑制剂(跨线治疗、新型抑制剂)、转换为其他靶向治疗[针对PI3K/AKT/mTOR通路的抑制剂、抗体-药物偶联物(ADC)、聚腺苷二磷酸核糖聚合酶(PARP)抑制剂、组蛋白去乙酰化酶(HDAC)抑制剂]及化疗等。临床需结合患者个体情况制定精准化治疗方案。本文就CDK4/6抑制剂在乳腺癌治疗中的耐药机制及应对策略研究进展进行综述。

关键词：细胞周期蛋白依赖性激酶4/6抑制剂；乳腺癌；耐药；人类表皮生长因子受体2；治疗策略

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Resistance mechanisms and coping strategies of CDK4/6 inhibitors in treatment of breast cancer

CHEN Guo*, HU Dandan, ZHANG Xiaoqing

*The First Clinical College, Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210023, China

Corresponding author: ZHANG Xiaoqing, E-mail: zxqing1983@163.com

Abstract: The standard first-line treatment for advanced hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer is the combination of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors and endocrine therapy, which significantly prolongs patients' progression-free survival. However, clinical resistance to CDK4/6 inhibitors severely impacts patients' prognosis. The resistance mechanisms of CDK4/6 inhibitors are complex, involving multiple dimensions such as abnormal cell cycle regulation, activation of growth factor receptors and signaling pathways, abnormal immune regulation, and autophagy activation. Current strategies to address resistance include diverse approaches: combination with other endocrine agents [selective estrogen receptor degraders (SERDs) and selective estrogen receptor covalent antagonists (SERCAs)], continuation use of CDK4/6 inhibitors (cross-line therapy and new-generation inhibitors), switching to alternative targeted therapies [PI3K/AKT/mTOR pathway inhibitors, antibody-drug conjugate (ADC), poly ADP-ribose polymerase (PARP) inhibitors, histone deacetylase (HDAC) inhibitors] and chemotherapy. Clinical practice requires tailoring precision treatment strategies based on individual patient characteristics. This article systematically reviews the research progress on the resistance mechanisms of CDK4/6 inhibitors in breast cancer and corresponding therapeutic strategies.

Keywords: Cyclin-dependent kinase 4/6 inhibitor; Breast cancer; Drug resistance; Human epidermal growth factor receptor 2; Treatment strategy

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乳腺癌的发病率位列全球女性恶性肿瘤首位，而激素受体(hormone receptor，HR)阳性/人类表皮生长因子受体2(human epidermal growth factor receptor 2，HER2)阴性这一分型的乳腺癌约占乳腺癌总体的70%[1]。目前，HR阳性乳腺癌患者需接受5~10年内分泌药物治疗，其中20%~40%的患者会因耐药出现复发转移[2]。目前治疗HR+/HER2-的无症状内脏转移

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通信作者：张晓清，E-mail：zxqing1983@163.com

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乳腺癌患者仍然首选内分泌治疗，细胞周期蛋白依赖性激酶4/6（cyclin-dependent kinase 4/6，CDK4/6）抑制剂在细胞周期抑制肿瘤细胞的增殖。目前《晚期乳腺癌国际共识指南（第五版）》[3]和美国国立综合癌症网络（NCCN）[4]推荐CDK4/6抑制剂联合内分泌治疗为HR+/HER2-乳腺癌进展期的标准治疗方案，CDK4/6抑制剂联合第三代芳香化酶抑制剂或选择性雌激素受体降解剂（selective estrogen receptor degraders，SERDs）氟维司群（fulvestrant）的方案作为晚期一、二线治疗HR+/HER2-乳腺癌的标准选择，能够显著延长患者的无进展生存期（progression-free survival，PFS）。目前已有四种CDK4/6抑制剂经国家药品监督管理局批准上市，分别为哌柏西利（palbociclib）、瑞波西利（ribociclib）、阿贝西利（abemaciclib）和达尔西利（dalpiciclib），联合内分泌药物治疗均显示出较好的临床疗效[5]。

然而，在晚期一线治疗中使用CDK4/6抑制剂联合芳香化酶抑制剂后PFS在2年左右[6]，由此可见，耐药极大地限制了其治疗效果，导致疾病进展，严重影响患者的预后。因此，深入研究CDK4/6抑制剂耐药后的治疗策略，对临床治疗具有重要的意义。

1　CDK4/6抑制剂耐药机制

*WEE*1和*MDM*2基因过表达，组蛋白去乙酰化酶（histone deacetylase，HDAC）活化，CDK2/4/6、cyclinE1扩增，Rb、FZR1、FAT非典型钙黏蛋白1蛋白功能丧失等，它们均可能使细胞周期进程异常，使肿瘤细胞对CDK4/6抑制剂的敏感性降低，从而产生耐药[7-8]。生长因子受体及信号通路的激活，如成纤维细胞生长因子受体（fibroblast growth factor receptor，FGFR）1、PI3K/AKT/mTOR通路等，均可促进肿瘤细胞的增殖，进而引发耐药。有研究证实，肿瘤细胞对CDK4/6抑制剂的耐药性可通过抑制异常FGFR活性来逆转[9]。

同时，有研究显示，在对哌柏西利耐药的细胞中，与T细胞的活化及杀伤相关的免疫调控关键基因发生突变的频率显著增高，相关的免疫基因突变后，CDK4/6抑制剂诱导免疫途径失控[10]，影响了肿瘤微环境中免疫细胞的功能和免疫相关分子的表达，使机体产生免疫逃逸，进而出现耐药。

除此之外，自噬的激活不仅可逆转CDK4/6抑制剂造成的细胞周期阻滞，也可参与CDK4/6抑制剂耐药的产生[11]，在乳腺癌细胞中具有双重作用。

2　CDK4/6抑制剂耐药后的治疗策略

2.1　联合其他内分泌药物

2.1.1　SERDs　SERDs可特异性地降解雌激素受体，从而阻断雌激素信号通路，达到抑制肿瘤生长的目的。氟维司群是一种选择性雌激素受体下调剂类内分泌药物，能够更加彻底地阻断雌激素受体及下游信号通路的转导。氟维司群在整体HR+/HER2-晚期乳腺癌人群的中位PFS为8.5个月（95%*CI*：7.0~10.0个月）[12]，CDK4/6抑制剂氟维司群联合用药相比于安慰剂联合氟维司群，可延长内分泌治疗耐药的乳腺癌患者的PFS（*HR*=0.51，*P*<0.05）和总生存期（overall survival，OS）（*HR*=0.73，*P*<0.05），尽管该治疗方法可能引发血液系统不良反应，但均在可耐受范围内[13]。

新一代口服SERDs［如艾拉司群（elacestrant）、giredestrant］在临床试验中显示出优于氟维司群的疗效，可显著延长雌激素受体突变患者的中位PFS（*HR*=0.55，*P*<0.05）[14]，但目前还没有CDK4/6抑制剂+艾拉司群联合用药的临床研究。《中国抗癌协会乳腺癌诊治指南与规范》认为，艾拉司群可用于治疗*ESR*1突变的HR+/HER2-晚期乳腺癌[15]。

2.1.2　选择性雌激素受体共价拮抗剂（selective estrogen receptor covalent antagonists，SERCAs）　乳腺癌内分泌耐药的主要机制是*ESR*1突变介导的非配体依赖活性，导致药物亲和力减弱。H3B-6545作为SERCAs的一种，能够不可逆地与雌激素受体α的半胱氨酸残基共价结合，从而恢复药物敏感性[16]。

Johnston等[17]应用H3B-6545联合哌柏西利治疗CDK4/6抑制剂耐药患者，患者中位PFS为11.5个月，12个月的总生存率为72.5%（95%*CI*：50.1%~86.1%）。Hamilton等[18]对H3B-6545单药的疗效进行评估，患者的中位PFS和OS分别达到5.06个月和21.52个月。上述研究证实，推荐剂量下的H3B-6545具有有效的初步抗肿瘤活性，然而目前H3B-6545尚处于临床Ⅱ期研究阶段，其是否能够安全有效地运用于临床还需要更多医学证据支持。

2.2　继续使用CDK4/6抑制剂

2.2.1　现有CDK4/6抑制剂跨线治疗　在PALOMA-3[19]、MONARCH 2[20]、MONALEESA-3[21]研究中，对于HR+/HER2-的晚期乳腺癌患者，分别选择了哌柏西利、阿贝西利和瑞波西利，联合氟维司群作为二线治疗方案，中位PFS均显著提高，分别达到11.2、16.4、20.5个月。对于一线CDK4/6抑制剂耐药患者的二线治疗选择，PACE研究表明，使用哌柏西利跨线治疗未取得阳性结果[22]，MAINTAIN和TRINITI-1研究表明，使用瑞波西利跨线治疗能够显著延长中位PFS[23-24]。2024年，在美国临床肿瘤协会会议上，postMONARCH研究报道了最新的数据，阿贝西利组和安慰剂组6个月无进展生存率分别为50%和37%，证实了使用阿贝西利联合氟维司群治疗可以显著改善患者的PFS（*P*=0.01）[25]。该研究中既往接受哌柏西利治疗的患者后线使用阿贝西利获益最为显著（*HR*=0.62），证实CDK4/6抑制剂治疗进展后改用另一种CDK4/6抑制剂是可行的治疗选择[25]。但该研究中既往使用阿贝西利的患者仅占8%，样本量较小，因此其结果尚不能证实同种CDK4/6抑制剂的再使用是否能够使耐药患者获益。Ravani等[26]综合统计18项研究发现，后线继续使用CDK4/6抑制剂治疗与更长的PFS（*HR*=0.64，*P*<0.01）和OS（*HR*=0.70，*P*<0.01）相关。此外，使用原CDK4/6抑制剂（*HR*=0.62，*P*<0.01）或改用不同的CDK4/6抑制剂（*HR*=0.49，*P*<0.01）均可使PFS获益。

上述研究提示，对于未检测到靶点突变或无法使用其他靶向药物进行治疗的患者，CDK4/6抑制剂的跨线治疗是一种合理且有效的治疗选择。同时，由于CDK4/6抑制剂耐药患者的异质性较高，CDK4/6抑制剂疗效受治疗人群及联合治疗方案等多因素影响，其选择应结合具体情况具体分析，治疗应更加个体化、精准化。

2.2.2 使用新型CDK4/6抑制剂或CDK4抑制剂 新一代CDK4/6抑制剂来罗西利(lerociclib,GB491)作为一种强效且具有选择性的口服CDK4/6抑制剂,在实验室研究中显示出对CDK4/cyclin D1和CDK6/cyclin D3的高度活性,以及对CDK9/cyclin T的中等活性。在Ⅲ期LEONARDA-1研究中显示,来罗西利联合氟维司群可将PFS延长至11.07个月(P<0.01),且安全性优于传统CDK4/6抑制剂[27]。

2024年欧洲肿瘤内科学会(European Society for Medical Oncology,ESMO)乳腺癌年会公布的新型CDK4抑制剂PF-07220060,在接受过CDK4/6抑制剂和内分泌药物治疗的HR+/HER2-转移性乳腺癌患者中,使用该CDK4抑制剂+来曲唑或氟维司群联合治疗,中位PFS为8.1个月,且产生的血液学不良事件较少,有较好的安全性,在CDK4/6抑制剂经治人群中可作为有潜力的新选择[28]。

2.3 *转换为其他靶向治疗*

2.3.1 针对PI3K/AKT/mTOR通路的联合治疗 PAM通路调节肿瘤细胞的生长和增殖,在约50%的晚期患者中能够观察到该信号通路的基因突变[29]。PI3K/AKT/mTOR通路在乳腺癌的发生发展中起关键作用,且与CDK4/6抑制剂耐药密切相关[30-31]。针对该通路的靶向药物,与CDK4/6抑制剂联合使用,已在临床研究中显示出一定的疗效。PAM通路抑制剂主要可分为PI3K抑制剂[如塔西利司(taselisib)、阿培利司(alpelisib)]、AKT抑制剂[如卡帕塞替尼(capivasertib)]和mTOR抑制剂[如依维莫司(everolimus)]。

依维莫司作为mTOR抑制剂,在Ⅲ期临床试验BOLERO-2中的结果显示,依维莫司联合依西美坦组的PFS显著延长(6.9个月 *vs* 2.8个月,P<0.01)[32]。虽然,依维莫司组的毒性也显著高于安慰剂组,但权衡益处与毒性后,依维莫司与依西美坦的联合使用仍可能成为治疗CDK4/6抑制剂耐药性乳腺癌的选项之一。BOLERO-5研究结果表明,绝经后中国女性乳腺癌患者使用依维莫司与依西美坦的联合治疗,可显著提升PFS,这进一步验证了BOLERO-2研究的临床效益,且其在中国患者中具有良好的安全性,大多数不良事件为轻度至中度,均可通过适当的剂量调整和对症治疗进行管理[33]。

伊那利塞(inavolisib)作为新一代PI3K抑制剂[34],在INAVO120研究先前的报道结果中显示出良好的疗效[35]。这项研究将伊那利塞联合哌柏西利和氟维司群,作用于内分泌治疗耐药且伴有*PIK3CA*突变的HR+/HER2-患者,结果显示,安慰剂组的PFS仅为7.3个月,伊那利塞组的PFS达到15.0个月。2024年美国临床肿瘤学会(American Society of Clinical Oncology,ASCO)年会上该研究更新了数据,伊那利塞组中位PFS延长至24.0个月,对照组为15.1个月[35]。美国食品药物监督管理局(Food and Drug Administration,FDA)于2024年10月批准了伊那利塞联合哌柏西利和氟维司群可用于治疗*PIK3CA*突变且辅助内分泌治疗耐药的HR+/HER2-的乳腺癌患者。

《中国临床肿瘤学会(CSCO)乳腺癌诊疗指南2024》[36]将AKT抑制剂联合内分泌治疗作为CDK4/6抑制剂治疗失败分层的Ⅲ级推荐。CAPItello-291试验将AKT抑制剂卡帕塞替尼联合氟维司群用于PIK3CA/AKT1/PTEN通路异常患者,受试者中有69.1%的患者先前接受过CDK4/6抑制剂治疗,结果显示该方案显著延长了HR+/HER2-的晚期乳腺癌患者的PFS,且安全性良好[37]。该研究结果为此治疗方案提供了有力的临床证据,表明其可作为HR+/HER2-晚期乳腺癌患者在CDK4/6抑制剂治疗失败后的选择。

2.3.2 抗体-药物偶联物(antibody-drug conjugate,ADC) ADC药物组成包括单克隆抗体、连接子和有效载荷,可将细胞毒性药物特异性地输送到肿瘤细胞内,精准杀伤肿瘤细胞[38]。

目前国际上用于治疗乳腺癌的新型ADC药物包括德曲妥珠单抗(trastuzumab deruxtecan,T-DXd)和戈沙妥珠单抗。人类滋养层细胞表面抗原2(trophoblast cell-surface antigen 2,Trop-2)是一种跨膜钙信号传递器,是靶向治疗中的一个新型且有前途的分子靶点[39]。戈沙妥珠单抗作为靶向Trop-2的ADC药物,其在TROPiCS-02研究中表现出了良好的疗效和安全性,中位PFS和OS分别达到5.5个月和14.4个月[40]。戈沙妥珠单抗用于治疗CDK4/6抑制剂治疗失败的HR+/HER2-晚期乳腺癌患者时,也被认为具有高于传统化疗单药的PFS和OS[15]。DESTINY-Breast06研究证实,T-DXd对比标准化疗治疗CDK4/6抑制剂耐药患者可带来显著PFS获益(13.2个月 *vs* 8.1个月)[41]。Dawood等[42]的研究发现对于CDK4/6抑制剂联合内分泌经治的晚期乳腺癌患者,使用T-DXd和戈沙妥珠单抗均可显著改善患者5年总生存率(T-DXd:74.8% *vs* 52.2%,P<0.05;戈沙妥珠单抗:73.4% *vs* 64.7%,P<0.05)。2023年ESMO指南推荐,对于一线CDK4/6抑制剂联合内分泌治疗后快速进展的患者,HER2低表达者可选择T-DXd,HER2-者可选择戈沙妥珠单抗。

德达博妥单抗是另一种TROP-2靶向的新型ADC药物,通过靶向传输细胞毒制剂至癌细胞内,减少细胞毒制剂的大范围蔓延。TROPION-Breast01研究结果显示,对于内分泌治疗耐药的HR+/HER2-晚期乳腺癌患者,德达博妥单抗组的中位PFS较对照组显著延长(6.9个月 *vs* 4.9个月,P<0.05)[43]。2024年欧洲肿瘤内科学会乳腺癌年会上更新了该研究的患者报告结局,德达博妥单抗组健康状况、生存质量、身体功能、疼痛等次要终点的恶化时间均显著延迟[44]。与传统方案相比,德达博妥单抗具有更好的疗效和可管理的安全性,能够有效提高患者的生存质量,是一种耐受性良好的治疗新选择。但抗Trop-2的ADC尚未在国内获批上市,仍需更多的临床试验证实其安全性与可行性。

2.3.3 聚腺苷二磷酸核糖聚合酶(poly ADP-ribose polymerase,PARP)抑制剂 DNA损伤包括DNA单链断裂(DNA single strand breaks,SSBs)和/或DNA双链断裂(DNA double strand breaks,DSBs)。PARP的18种亚型中仅PARP1及PARP2能修复DNA损伤,若PARP缺失导致DNA修复不及时或不正确,染色体会产生突变或畸变。PARP抑制剂则可抑制PARP的功能,干扰细胞的DNA单链损伤修复,从而抑制细胞DNA复制,当其作用于肿瘤细胞时可以达到抗癌的目的。

乳腺癌易感基因(breast cancer associated gene,*BRCA*)1/2

是重要的抑癌基因，通过基因重组修复双链损伤的正常细胞DNA，其突变会导致基因组的不稳定从而引发卵巢癌、乳腺癌等肿瘤的发生，其中*BRCA*2突变主要见于HR阳性乳腺癌，复发风险较高[45]。胚系*BRCA*突变乳腺癌患者生存结局差，死亡风险高，故在发病早期对突变高风险人群进行基因检测十分重要。

鉴于*PARP*和*BRCA*1/2二者之一缺失后肿瘤细胞仍可复制，当患者*BRCA*1/2缺陷或丢失时，使用PARP抑制剂可阻断单链断裂DNA的损伤修复，二者双重打击可导致肿瘤细胞因单、双链均无法修复而凋亡[46]，这也是PARP抑制剂治疗*BRCA*突变肿瘤的基础。PARP抑制剂可促进非同源末端的连接，增加修复的错误率[47]，阻碍肿瘤细胞增殖。因此，若未接受BRCA等遗传易感基因检测的HR+/HER2−乳腺癌患者经内分泌治疗耐药后，建议行基因检测，若*BRCA*突变，优选PARP抑制剂。

目前上市的PARP抑制剂药物有奥拉帕利等。奥拉帕利作为PARP抑制剂的主要代表药物，于2018年1月和2019年3月分别被FDA和欧洲药品管理局批准用于治疗胚系*BRCA*1/2突变、HER2−（gBRCAm/HER2−）的局部晚期或转移性乳腺癌，2022年3月被FDA批准用于既往接受过新辅助或辅助化疗的携带gBRCAm/HER2−的高危早期乳腺癌成人患者的辅助治疗，为奥拉帕利精准治疗早期和晚期乳腺癌提供了新的选择。

目前奥拉帕利治疗*BRCA*突变HER2−转移性乳腺癌的Ⅲ期临床试验，与标准化疗方案相比，奥拉帕利单药治疗组的中位PFS延长了2.8个月，疾病进展或死亡风险降低了42%（$P<0.05$）[48]，中位OS达到19.3个月（$P<0.05$）[49]，表明奥拉帕利组的疗效明显优于标准单药化疗组。

《中国抗癌协会乳腺癌诊治指南与规范（2024年版）》[15]指出，PARP抑制剂奥拉帕利等可作为胚系*BRCA*1或*BRCA*2突变的晚期乳腺癌治疗的可选方案，但国内尚未获批适应证。

2.3.4 HDAC抑制剂 研究发现，在HR+乳腺癌细胞中，HDAC抑制剂可抑制雌激素受体及其应答基因的转录，在HR−乳腺癌细胞中，HDAC抑制剂可促进雌激素受体的表达，提示HDAC抑制剂具有增强、恢复抗雌激素治疗效果的作用[50]。目前，已有临床试验将HDAC抑制剂用于HR+乳腺癌的内分泌治疗中，可逆转内分泌治疗的耐药性[51]。

西达本胺（tucidinostat，苯酰胺类HDAC亚型选择性抑制剂）是国内首批上市的HDAC抑制剂。一项真实世界研究发现，CDK4/6抑制剂进展后接受过西达本胺治疗的HR+/HER2−转移性乳腺癌患者中，即刻使用西达本胺治疗患者的中位PFS达到了4.5个月，而总人群患者的中位PFS仅2.0个月[51]。2019年西达本胺联合芳香化酶抑制剂获批用于HR+、HER2−、绝经后、经内分泌治疗复发或进展的局部晚期或转移性乳腺癌患者。因此，中国临床肿瘤学会指南推荐西达本胺联合依西美坦作为曾接受过他莫昔芬和/或非甾体类芳香化酶抑制剂治疗失败的HR+乳腺癌患者的治疗方案。

恩替司他是第1个在乳腺癌Ⅱ期临床研究中被认为有治疗效果的HDAC抑制剂。Yardley等[52]研究发现，恩替司他联合依西美坦治疗芳香化酶抑制剂治疗进展的HR+/HER2−转移性乳腺癌130例患者的疗效优于依西美坦单药组（PFS延长2个月，OS延长8.3个月）。然而，Connolly等[53]研究发现，恩替司他联合依西美坦治疗芳香化酶抑制剂治疗进展的HR+/HER2-转移性乳腺癌608例患者的疗效与依西美坦单药组相类似（PFS：3.3个月 *vs* 3.1个月；OS：23.4个月 *vs* 21.7个月）。因此，对于芳香化酶抑制剂治疗后进展的晚期HR+/HER2-乳腺癌患者的内分泌治疗中加入恩替司他能否提高生存率存在争议。

为了验证恩替司他在中国乳腺癌患者中的疗效和安全性，我国学者开展了Ⅲ期临床试验，研究结果显示，既往经内分泌治疗复发或进展的局部晚期或转移性乳腺癌患者的恩替司他联合依西美坦组PFS显著长于安慰剂组（6.32个月 *vs* 3.72个月），降低了24%的疾病进展或死亡风险（*HR*=0.76，P=0.046），恩替司他组中位OS为38.55个月，较安慰剂组延长超过9个月，降低死亡风险25%（*HR*=0.75），显示出了较好的生存获益[54]。CDK4/6抑制剂耐药患者和既往接受过化疗的患者中同样显示出较好的疗效。此外，恩替司他在无内脏转移、原发内分泌耐药、既往未使用过氟维司群的患者中获益更明显。

2024年4月30日，国家药品监督管理局批准恩替司他片的适应证为：联合芳香化酶抑制剂治疗HR+、HER2−以及经内分泌治疗复发或进展的局部晚期或转移性乳腺癌患者。

2.4 *转换为化疗* HR+/HER2-乳腺癌因药物敏感性差异，在新辅助化疗后达到病理完全缓解（pathological complete response，pCR）的比例明显低于其他亚型[55]。但是，HR+/HER2−乳腺癌中Ki-67越高，表明更多的细胞处于增殖期，此类患者往往对化疗更加敏感[56]。此外，HR+患者内分泌治疗耐药后，出现有症状的内脏转移，仍可接受化疗，但其主要目的为缓解全身症状，提高生活质量，延长生存期。因此，化疗在CDK4/6抑制剂耐药后的治疗中仍具有重要作用。常用的化疗方案包括蒽环和/或紫杉类、卡培他滨、铂类等，可使用单药也可联合治疗。化疗在控制肿瘤生长、缓解症状的同时，不良反应也较大，如骨髓抑制、胃肠道反应等。因此，在化疗过程中，需密切关注患者的不良反应，并采取相应的应对策略，如补充益生菌、艾灸联合穴位贴敷治疗、针刺疗法等。

Kim等[57]在研究人群中纳入了绝经前局部晚期HR+/HER2-乳腺癌的患者，结果显示，相较于单独化疗，新辅助化疗联合卵巢功能抑制治疗患者显著提高了pCR率且降低了Ki-67表达。研究显示，新辅助化疗联合卵巢功能抑制，可以明显改善≤35岁的年轻HR+/HER2-乳腺癌患者的无病生存期[58]。因此，临床对于年轻HR+/HER2−局部晚期乳腺癌患者，建议新辅助化疗中可加用卵巢功能抑制治疗。

3 讨 论

近年来，HR+乳腺癌的治疗已经取得长足进展，特别是CDK4/6抑制剂联合内分泌治疗，显著改善了患者的PFS和OS。但是，CDK4/6抑制剂耐药这一问题的出现，给临床治疗

带来了挑战。所幸针对这一困境，现已探寻出多种有效的治疗方法。

对于多数患者，跨线使用CDK4/6抑制剂联合内分泌治疗，能够显著延长PFS。与此同时，新型CDK4/6抑制剂的研发不断探索和优化了药物结构和作用机制，旨在克服现有药物的耐药问题，提高疗效，其潜力令人期待。合理搭配作用于激素受体信号通路不同环节的内分泌药物、转换为其他靶向治疗、联合化疗，发挥三者的协同作用，亦可提高治疗效果。虽然肿瘤患者的个体差异较大，但在临床实践中，医生会根据患者的具体情况，制定个性化的联合方案，以在达到最佳治疗效果的同时，减少不良反应，延长患者生存期的同时，减轻患者痛苦。

总体而言，CDK4/6抑制剂耐药后多种不同的治疗方法都各有优势，也为患者提供了多样化的治疗选择。

利益冲突　无

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