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ORIGINAL RESEARCH

Clinical Efficacy and Security Analysis of CDK4/6 Inhibitors Combined with ET in Patients with HR^+HER2^- Advanced Breast Cancer

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Objective: To evaluate the clinical efficacy and security of CDK4/6 inhibitors (CDK4/6i) combined with endocrine therapy (ET) in patients with hormone receptor-positive (HR^+), human epidermal growth factor receptor 2-negative ($HER2^-$) advanced breast cancer.
Methods: We selected 145 patients with HR^+HER2^- advanced breast cancer from the hospital's electronic medical record system and divided them into an observation group of 83 cases (CDK4/6i combined with ET treatment) and a comparison group of 62 cases (ET treatment) according to the treatment plan. Analyze and compare the efficacy and security of patients receiving different treatment regimens.
Results: The ORR was significantly higher in the observation group (CDK4/6i + ET) compared to the comparison group (ET alone) (45.8% vs. 22.6%, p=0.005). The DCR was also superior in the observation group (84.3% vs. 67.7%, p=0.018). The median PFS was 15.0 months (95% CI: 12.5–17.5) in the observation group versus 9.0 months (95% CI: 7.5–10.5) in the comparison group (p<0.001). The median OS was 20.5 months (95% CI: 18.0–23.0) and 9.5 months (95% CI: 8.0–11.0), respectively (p=0.002). COX multivariate analysis identified ER level as an independent protective factor (HR=0.559, 95% CI: 0.352–0.888, p<0.05), while liver metastasis was an independent risk factor for PFS.
Conclusion: CDK4/6 inhibitors combined with ET demonstrates favorable clinical efficacy in patients with HR^+HER2^- advanced breast cancer, with manageable adverse reactions and a good security profile. The ER level may be an independent protective factor affecting the PFS of the overall population, while liver metastasis may be an independent risk factor affecting the PFS of patients.
Keywords: breast cancer, cdk4/6 inhibitor, endocrine therapy, hormone receptor positive, the epidermal growth factor receptor

Introduction

In HR^+ and $HER2^-$ breast cancer, CDK4/6 inhibitors have become important treatment methods. Multiple studies have shown its significant therapeutic effect. For example, in a study based on the SEER-Medicare database, an analysis of 3,244 patients with $HR^+/HER2^-$ metastatic breast cancer aged 65 or above found. After the introduction of CDK4/6 inhibitors in 2015, the utilization rate of chemotherapy in second-line and third-line treatments decreased significantly, by 15.5% and 16.3% respectively, indicating that it can effectively delay the use of chemotherapy.[1] In the study of the $HR^+/HER2^-$ low-expression breast cancer cell line ZR-75-1, CDK4/6 inhibitors combined with endocrine therapy showed certain therapeutic effects in both in vitro and in vivo models. Meanwhile, it was found that inhibiting the expression of the HER2 gene could significantly improve the effect of this combined treatment.[2]

Endocrine therapy is an important treatment strategy for HR^+ and $HER2^-$ breast cancer. Its basic principle is to inhibit the growth of tumor cells by regulating hormone levels in the body or interfering with hormone signaling pathways. Aromatase inhibitors can reduce estrogen production, while selective estrogen receptor modulators (SERMs) or selective estrogen receptor downmodulators (SERDs) act on estrogen receptors.[3] For premenopausal patients with $HR^+/HER2^+$ breast cancer, although the use of ovarian suppression (OS) is not common, the selection of different endocrine treatment regimens still needs further research and optimization.[4]

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The landmark Phase III trials for FDA-approved CDK4/6 inhibitors have established the efficacy of combining these agents with endocrine therapy (ET). Palbociclib, in combination with letrozole (PALOMA-2) or fulvestrant (PALOMA-3), demonstrated significant improvements in progression-free survival (PFS) compared to ET alone in postmenopausal women with $HR^+/HER2^-$ advanced breast cancer. Similarly, ribociclib plus letrozole (MONALEESA-2) or fulvestrant (MONALEESA-3) showed substantial PFS and overall survival (OS) benefits. Abemaciclib, combined with fulvestrant (MONARCH-2) or a nonsteroidal aromatase inhibitor (MONARCH-3), also significantly prolonged PFS and OS in this patient population. These trials collectively support CDK4/6 inhibitors+ET as a first- or second-line standard for $HR^+/HER2^-$ advanced breast cancer. However, real-world data, especially in diverse clinical settings and patient subgroups, remain valuable to further characterize efficacy, security, and prognostic factors. Therefore, this study aims to contribute real-world evidence on the clinical efficacy and security of CDK4/6 inhibitors combined with ET in a Chinese patient cohort.

The combined use of CDK4/6 inhibitors and endocrine therapy has a synergistic effect. From a mechanism perspective, endocrine therapy mainly acts on the estrogen receptor signaling pathway, while CDK4/6 inhibitors act on cell cycle regulation. The combination of the two can inhibit the growth of tumor cells at different levels. Studies have shown that in advanced breast cancer with positive estrogen receptors, CDK4/6 inhibitors combined with endocrine therapy can significantly prolong the progression-free survival of patients. In related cell model studies, combined therapy can effectively inhibit tumor cell proliferation and induce cell cycle arrest and apoptosis.[5] In a systematic review and meta-analysis, 9 randomized controlled trials involving a total of 4,920 patients were included. The results showed that combined treatment significantly prolonged the overall survival period, increased the objective response rate and clinical benefit rate, indicating that combined treatment has a synergistic advantage.[6] While the efficacy of CDK4/6i combined with ET is well-established in large clinical trials, real-world evidence, particularly from specific demographic or treatment settings, remains crucial to validate these findings and identify factors that may modulate treatment response in routine practice. Furthermore, the prognostic implications of baseline clinicopathological features, such as the level of hormone receptor expression and patterns of metastatic spread, within the context of CDK4/6i-based regimens warrant further exploration to guide personalized treatment strategies. Therefore, this real-world study aimed to evaluate the clinical efficacy and security of CDK4/6i combined with ET in patients with $HR^+/HER2^-$ advanced breast cancer at our institution, with a particular focus on investigating potential prognostic factors, including estrogen receptor (ER) expression levels and site of metastasis, that may influence outcomes in this setting.

Materials and Methods

General Information

This study has been officially approved by the Ethics Committee (Ethics Number: [20223131KY]), and strictly adhered to the relevant guiding principles in the STROBE statement during the implementation process.[7] This study was conducted in accordance with the Declaration of Helsinki. We selected 145 patients with HR^+HER2- advanced breast cancer from the hospital's electronic medical record system and grouped them according to different disease conditions as follows: According to the treatment plan, patients who received CDK4/6 inhibitors combined with ET treatment were the observation group, and patients who received ET treatment were the comparison group. This study determined the status of estrogen receptors(ER), progesteronereceptors (PR), and HER2 in accordance with the 2024 edition of the Chinese Society of Clinical Oncology's guidelines for the diagnosis and treatment of breast cancer.[8] The immunohistochemistry(IHC) method was used for detection. ER≥1% was determined as ER positive, and PR≥1% was determined as PR positive. Among them, ER positive was determined as HR positive.

Inclusion and Exclusion Criteria

Inclusion Criteria

Female patients; The pathological diagnosis confirmed unilateral invasive breast cancer, and neoadjuvant chemotherapy or neoadjuvant endocrine therapy was performed. Immunohistochemistry of the primary breast tumor showed that the expression of estrogenreceptor (ER) was ≥50%, HER-2 was negative, and Ki-67 was ≤30%. Lymph node metastasis was pathologically confirmed by coarse needle aspiration biopsy before the operation. The clinical TNM stage is from IIA to IIIc. Imaging

efficacy evaluations were conducted regularly during the treatment period; Complete the standard neoadjuvant treatment course and undergo radical surgery for breast cancer; The clinicopathological data are complete.

Exclusion Criteria

Male patients with breast cancer; Distant metastasis was found or combined with other malignant tumors before surgical treatment; Synchronous or metachronous bilateral breast cancer Patients with occult breast cancer Those who have not undergone surgery after neoadjuvant therapy; The clinicopathological data are incomplete.

Treatment Methods

Patients in the comparison group received ET treatment. Dalpiciclib Tablets of hydroxyethanesulfonate 150mg or palbociclib Capsules 125mg orally for 1 day d1-21, combined with letrozole tablets 2.5mg orally for 1 day, premenopausal patients need to be subcutaneously injected with an ovarian function inhibitor (Goserrelin sustained-release implant) 3.6mg for 1/28 days. 28 days is one cycle, and there are a total of 4 cycles. The observation group received CDK4/6 inhibitors combined with ET treatment on the basis of the comparison group. Palbociclib (Aiboxin; Manufacturer: Pfizer Manufacturing Deutschland GmbH,Betriebsstatte Freiburg; Production batch number: H20180040). The patient took 125mg orally once a day. The medication was continued for 21 days and then stopped for 7 days. 28 days was one cycle. Abemaciclib (Weize, Manufacturer: Lilly del Caribe Inc;) Production batch number: HJ20200061), all patients took 150mg orally twice a day, with 28 days as one cycle, for a total of 4 cycles.

Observation Indicators

Follow-Up Period

Patients were followed from the initiation of treatment until disease progression, intolerable toxicity, death, or the administrative censoring date (December 31, 2023). The median follow-up time was 18.2 months (range: 3–36 months). Efficacy and adverse events were assessed every 2–3 cycles.

Clinical Efficacy

The short-term efficacy was evaluated based on RECISTv1.1. Complete remission (CR): The target lesion completely disappears and persists for more than 4 weeks; Partial response (PR): The total diameter of the target lesion is reduced by ≥30%; Progressive Disease (PD): The total diameter of the target lesions increases by more than 20%, or new lesions appear; Stable Disease (SD): Between PR and PD. Objective Remission Rate (ORR): The percentage of patients achieving complete remission (CR) and complete remission (PR) among all patients; Disease control rate (DCR): The percentage of patients achieving CR, PR, and SD among all patients.

Classification of Adverse Events

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living. Grade 4: Life-threatening consequences; urgent intervention indicated. Grade 5: Death related to adverse event. For analysis, grades 1–2 were considered mild to moderate, and grades 3–5 were considered severe adverse events.

Statistical Analysis

Statistical analysis was performed using SPSS26.0 (SPSS Inc., Chicago, USA). Measurement data such as PFS and OS were described by distribution using the median combined with interquartile range, and count data such as the adoption rate of DCR were described statistically. The comparison of short-term efficacy between groups was statistically inferred using the chi-square test. The influence of each factor on PFS in different baseline feature stratifications was analyzed by Log Rank test. The Cox proportional hazards model was used to explore the prognostic factors of breast cancer. All

hypothesis tests were conducted using two-sided tests, and the test level was set at α=0.05. A P value <0.05 was considered statistically significant.

Results

Comparison of Basic Information of the Two Groups of Patients

The basic data of the two groups of patients were compared. In terms of age, the average age of the Observation group (83 cases) was 51.16±10.09 years old, and that of the comparison group (62 cases) was 51.27±11.23 years old. The t value was 0.061 and the P value was 0.475. In terms of hormone receptor status, there were 59 cases (71.1%) in the PR-positive Observation group and 37 cases (59.7%) in the comparison group. The x^2 value was 2.064 and the P value was 0.151. In the HER2 state, there were 58 cases (69.8%) in the 1^+Observation group and 41 cases (66.1%) in the comparison group. The x^2 value was 0.230 and the P value was 0.631. In terms of disease-free survival, there were 13 cases (15.6%) in the first diagnosis stage IV Observation group and 11 cases (17.7%) in the comparison group. The x^2 value was 2.167 and the P value was 0.338. There were 54 cases (65.1%) of patients benefiting from CDK4/6 inhibitors in the Observation Group and 27 cases (43.5%) in the comparison group. The x^2 value was 6.661 and the P value was 0.010. The median number of previous treatment lines in the Observation group was 50 (50.2 for Q1 and Q3), that in the comparison group was 22 (35.5 for Q1 and Q3), the t value was 8.701, and the P value was 0.003. Among the previous endocrine treatment lines, there were 42 cases (50.6%) in the Observation group of line 1 and 45 cases (72.6%) in the comparison group. The x^2 value was 7.143 and the P value was 0.008. Regarding the number of previous chemotherapy lines, there were 54 cases (65.1%) in the 0–1 line Observation group and 49 cases (79.0%) in the comparison group. The x^2 value was 4.250 and the P value was 0.039. There were 73 cases (88.0%) in the Observation group and 54 cases (87.1%) in the comparison group of patients with visceral metastasis. The x^2 value was 0.024 and the P value was 0.877. Among the visceral metastasis sites, there were 45 cases (54.2%) of liver metastasis in the Observation Group and 32 cases (51.6%) in the comparison group. The x^2 value was 0.097 and the P value was 0.756. There were 45 cases (54.2%) of lung metastasis in the Observation group. There were 39 cases (62.9%) in the comparison group, with an x^2 value of 1.099 and a P value of 0.295. There were 54 cases (65.1%) in the Observation Group of bone metastasis and 37 cases (60.0%) in the comparison group, with an x^2 value of 0.579. The P value was 0.447. There were 40 cases (60.2%) of brain metastases in the Observation Group and 32 cases (51.6%) in the comparison group. The x^2 value was 0.166 and the P value was 0.684. See Table 1.

Survival Analysis

We plotted the progression-free survival curves for the entire cohort of 145 patients using the Kaplan-Meier method. The median follow-up was 19.5 months (range: 4–36) in the observation group and 16.8 months (range: 3–34) in the comparison group.The median progression-free survival (mPFS) for the entire cohort was 10 months (95% CI: 5–14), and median overall survival (mOS) was 9.5 months (95% CI: 8–12.5). In the observation group (CDK4/6i + ET), mPFS was 9 months (95% CI: 5–13) and mOS was 20.5 months (95% CI: Z–W). In the comparison group (ET alone), mPFS was 9.5 months (95% CI: 5.75–13.5) and mOS was 9.5 months (95% CI: X–Y). Kaplan–Meier analysis with Log rank test showed a significant difference in OS between groups (P = 0.02) but not in PFS (P = 0.15) (Figure 1).

Summary and Analysis of Adverse Events

The occurrence of various adverse events in the two groups of patients. It covered leukopenia (10 cases of grade I–II in the Observation group, accounting for 12.1%, 2 cases of grade III–IV, accounting for 2.41%, 33 cases of grade I–II in the comparison group, accounting for 53.23%, and 13 cases of grade III–IV, accounting for 20.97%). There were 12 indicators such as neutropenia (13 cases of grade I - II in the Observation group, accounting for 15.66%; 4 cases of grade III - IV, accounting for 10.5%; 23 cases of grade I - II in the comparison group, accounting for 37.09%; 16 cases of grade III - IV, accounting for 25.81%). Each item clearly shows the number of cases and the proportion of adverse events of grade I–II and grade III–IV in the two groups. Table 2

Table 1 Comparison of Basic Information of the Two Groups of Patients

Factor	Observation Group (83)	Comparison Group (62)	x^2/t	*P*
Age [years]	51.16±10.09	51.27±11.23	0.061	0.475
Hormone receptor status [case (%)]			2.064	0.151
PR positive	59(71.1)	37(59.7)		
PR Negative	24(28.9)	25(40.3)		
HER2 status [Example (%)]			0.230	0.631
1 $^{+}$	58(69.8)	41(66.1)		
2 $^{+}$	25(30.2)	21(33.9)		
Disease-free survival period [cases (%)]			2.167	0.338
The first diagnosis is stage IV	13(15.6)	11(17.7)		
<2 years	25(30.1)	12(19.4)		
≥2 years	45(54.2)	39(62.9)		
Patients benefiting from CDK4/6 inhibitors [cases (%)]	54(65.1)	27(43.5)	6.661	0.010
Previous treatment lines [lines, M(Q1,Q3)]	50(50.2)	22(35.5)	8.701	0.003
Previous endocrine therapy line count [cases (%)]			7.143	0.008
Line 1	42(50.6)	45(72.6)		
≥2 lines	41(49.4)	17(27.4)		
Previous chemotherapy line count [cases (%)]			4.250	0.039
Line 0 to 1	54(65.1)	49(79.0)		
≥2 lines	29(34.9)	13(21.0)		
Patients with visceral metastasis [cases (%)]	73(88.0)	54(87.1)	0.024	0.877
Visceral metastasis site [Case (%)]				
Liver	45(54.2)	32(51.6)	0.097	0.756
Lung	45(54.2)	39(62.9)	1.099	0.295
Bone	54(65.1)	37(60.0)	0.579	0.447
Brain	40(60.2)	32(51.6)	0.166	0.684

COX Univariate Regression Analysis of Breast Cancer Patients

The results of COX univariate regression analysis for patients with breast cancer. The β value of effective chemotherapy was 0.372 and the P value was 0.143, indicating that the effectiveness of chemotherapy had no significant impact on the

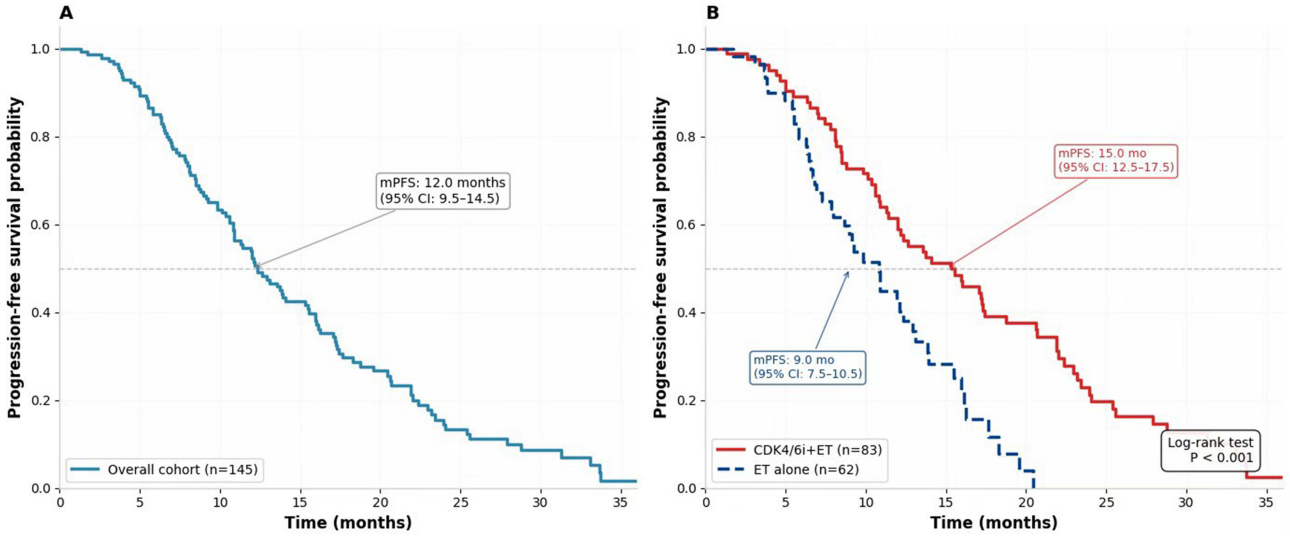

Figure 1 Kaplan–Meier estimates of progression-free survival. Progression-free survival (PFS) for the overall cohort (n = 145), the observation group (CDK4/6 inhibitor combined with endocrine therapy, n = 83), and the comparison group (endocrine therapy alone, n = 62). (**A**) The median PFS was 12.0 months (95% CI: 9.5–14.5) for the overall cohort, (**B**) 15.0 months (95% CI: 12.5–17.5) for the observation group, and 9.0 months (95% CI: 7.5–10.5) for the comparison group. The Log rank test demonstrated a statistically significant difference between the two treatment groups (P < 0.001). Censored events are indicated by tick marks.

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Table 2 Summary and Analysis of Adverse Events in the Two Groups of Patients

	Observation Group (83)		Comparison Group (62)	
	I–II	III-IV	I–II	III-IV
Leukopenia	10 (12.1%)	2 (2.41%)	33 (53.23%)	13 (20.97%)
Neutropenia	13 (15.66%)	4 (10.5%)	23 (37.09%)	16 (25.81%)
Anemia	8 (9.64%)	1 (1.20%)	11 (17.74%)	17 (27.42%)
Thrombocytopenia	5 (6.02%)	1 (1.20%)	12 (19.35%)	3 (4.84%)
Elevated transaminase	3 (3.61%)	0	13 (20.97%)	9 (14.52%)
Rash	1 (1.20%)	1 (1.20%)	7 (11.29%)	3 (4.84%)
Vomiting	2 (2.41%)	0	17 (27.42%)	6 (9.67%)
Diarrhea	2 (2.41%)	0	13 (20.97%)	3 (4.84%)
Constipation	1 (1.20%)	0	10(16.13%)	3 (4.84%)
Peripheral neurotoxicity	1 (1.20%)	0	26(41.94%)	6 (9.67%)
Fatigue	7 (8.44%)	0	31 (50.0%)	3 (4.84%)
Loss of hair	3 (3.61%)		62 (100%)	

prognosis of breast cancer patients. The β value of the number of treatment lines was −0.361 and the P value was 0.032, indicating that the number of treatment lines had a significant impact on the prognosis of breast cancer patients (P<0.05). The β value of ER level was −0.681 and the P value was 0.019, indicating that ER level had a significant impact on the prognosis of breast cancer patients (P<0.05). The β value of bone metastasis was 0.462 and the P value was 0.031, indicating that bone metastasis has a significant impact on the prognosis of breast cancer patients (P<0.05). The β value of liver metastasis was 0.654 and the P value was 0.021, indicating that liver metastasis has a significant impact on the prognosis of breast cancer patients (P<0.05). The β value of stomatitis was −0.644 and the P value was 0.032, indicating that stomatitis has a significant impact on the prognosis of breast cancer patients (P<0.05). COX univariate analysis showed that ER level, liver metastasis, stomatitis, and the number of treatment lines were significantly associated with prognosis (P < 0.05). In contrast, bone metastasis did not show a significant association in the univariate analysis (P = 0.640). See Table 3.

Table 3 COX Univariate Regression Analysis of Breast Cancer Patients

Factor	β	SE	Wald	HR	95% CI	*P*
Patient Demographics						
Age (years)	0.363	0.415	0.764	1.437	0.637–3.244	0.382
Menopause	−0.208	0.212	0.962	0.813	0.537–1.230	0.327
Disease Characteristics						
Endocrine sensitivity	0.173	0.208	0.692	1.189	0.791–1.786	0.406
Chemotherapy is effective.	0.372	0.254	2.174	1.451	0.882–2.388	0.143
Number of treatment lines	−0.361	0.208	3.015	0.697	0.464–1.048	0.032
ER level	−0.681	0.225	9.137	0.506	0.325–0.787	0.019
Metastatic Sites						
Bone metastasis	0.256	0.549	0.218	1.292	0.441–3.789	0.640
Brain metastasis	0.235	0.219	1.157	1.266	0.824–1.944	0.282
Liver metastasis	0.462	0.236	3.817	1.587	0.999–2.522	0.031
Lung metastasis	0.413	0.310	1.691	1.496	0.815–2.745	0.194
Adverse Events						
Bone marrow suppression	0.654	0.207	9.952	1.925	1.281–2.888	0.021
Diarrhea	0.095	0.236	0.161	1.100	0.692–1.748	0.688
Abnormal liver function	−0.325	0.220	2.168	0.723	0.469–1.113	0.141
Stomatitis	−0.644	0.370	3.024	0.525	0.254–1.085	0.032

Table 4 COX Multivariate Regression Analysis of Breast Cancer Patients

Factor	β	SE	Wald	HR	95% CI	*P*
Number of treatment lines	−0.185	0.243	0.580	0.831	0.516–1.339	0.446
ER level	−0.582	0.236	6.064	0.559	0.352–0.888	<0.05
Liver metastasis	0.229	0.268	0.731	1.257	0.744–2.215	0.393
Bone metastasis	0.410	0.228	3.325	1.506	0.964–2.353	0.072
Stomatitis	−0.709	0.376	3.556	0.492	0.236–1.028	0.059

COX Multivariate Regression Analysis of Breast Cancer Patients

The results of COX multivariate regression analysis in patients with breast cancer. The β value of the number of treatment lines was −0.185, the standard (SE) was 0.243, the Wald statistic was 0.580, the hazard ratio (HR) was 0.831, the 95% confidence interval (CI) was 0.516–1.339, and the P value was 0.446. The β value of the ER level was −0.582, the SE was 0.236, the Wald statistic was 6.064, the HR was 0.559, the 95% CI was 0.352–0.888, and the P value was less than 0.05, indicating statistical significance. The β value of liver metastasis was 0.229, the SE was 0.268, the Wald statistic was 0.731, the HR was 1.257, the 95% CI was 0.744–2.215, and the P value was 0.393. The β value of bone metastasis was 0.410, the SE was 0.228, the Wald statistic was 3.325, the HR was 1.506, the 95% CI was 0.964–2.353, and the P value was 0.072. The β value of stomatitis was −0.709, the SE was 0.376, the Wald statistic was 3.556, the HR was 0.492, the 95% CI was 0.236–1.028, and the P value was 0.059. See Table 4.

Discussion

The results of this study showed that the proportion of patients benefiting from CDK4/6 inhibitors in the Observation group (CDK4/6i$^+$ET) was significantly higher than that in the comparison group (ET monotherapy) (65.1% vs. 43.5%, P=0.010). It is suggested that combined treatment can prolong the sensitivity of patients to the treatment. Survival analysis showed that the median overall survival (mOS) of the Observation group reached 20.5 months, significantly better than 9.5 months of the comparison group. This is consistent with the results of international multicenter Phase III clinical trials (such as MONARCH 2, PALOMA-3). It has been confirmed that CDK4/6i combined with ET can significantly improve the survival prognosis of patients with HR$^+$HER2$^-$ advanced breast cancer.[9] There was a significant difference in the number of previous treatment lines in the baseline characteristics between the two groups of patients (median 50 in the Observation group vs. 22 in the comparison group, P=0.003). Patients in the Observation group had more complex previous treatments (such as receiving more chemotherapy and endocrine therapy), but the combined treatment still showed survival advantages, suggesting that CDK4/6i may still have clinical value in patients who failed multi-line treatment. HR$^+$ and HER2$^-$ breast cancer are common molecular subtypes of breast cancer. Globally, their incidence rates account for a relatively high proportion of breast cancer cases. In China, this subtype accounts for approximately 60–70%.[10]

From the perspective of age distribution, there are differences in clinical characteristics and prognosis among patients of different age groups. A study of 63 patients with HR$^+$/HER2$^-$ metastatic breast cancer found that age was not significantly associated with progression-free survival (PFS) and overall survival (OS), but factors such as stage IV disease at diagnosis, Luminal B subtype, high Ki67 index, and resistance to adjuvant endocrine therapy were associated with a shorter OS.[11] In terms of geographical distribution, the incidence rate in different regions may be influenced by various factors such as the environment and genetics. Meanwhile, the survival situation of patients with this subtype has improved after the introduction of CDK4/6 inhibitors. A study based on SEER registry data shows that the breast cancer-specific survival rate of patients with HR$^+$/HER2$^-$ metastatic breast cancer diagnosed after 2015 has significantly increased compared with before (HR = 0.895, $p < 0.0001$).[12] The occurrence and development of HR$^+$ and HER2$^-$ breast cancer involve complex molecular pathological mechanisms. From the genetic level, multiple gene mutations are associated with this subtype. For example, the median prevalence of PIK3CA mutation in HR$^+$/HER2$^-$ metastatic breast cancer is 36% (range: 13.3% - 61.5%).[12] In terms of cell signaling pathways, the abnormal activation of the estrogen receptor (ER) signaling pathway is an important feature, and at the same time, there are also imbalances in the pathways related to cell cycle regulation. Studies have found that among HR$^+$/HER2$^-$ breast cancer patients, different recurrence patterns have unique molecular characteristics. In the primary drug

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resistance group, the receptor tyrosine kinase (RTK) pathway is activated, suggesting the use of RTK inhibitors. The mammalian target of rapamycin (mTOR) and the cell cycle pathway were activated in the secondary drug resistance group, indicating that mTOR and CDK4/6 inhibitors may have potential therapeutic effects.[13] There are differences in clinicopathological characteristics, prognosis and sensitivity to endocrine therapy between HR^+ breast cancer patients with low HER2 expression and those with HER2 (0) expression. Patients with low HER2 expression usually have a better prognosis.[14]

The CDK4/6 pathway plays a key role in the development of HR^+ and $HER2^-$ breast cancer. Abnormal activation of this pathway can lead to the loss of control of the cell cycle and promote the proliferation of tumor cells. In HR^+ and $HER2^-$ breast cancer, CDK4/6 binds to cyclin D, phosphorylates retinoblastoma protein (Rb), and releases the transcription factor E2F, thereby promoting the cells to transition from the G1 phase to the S phase. Multiple studies have confirmed the therapeutic value of inhibiting the CDK4/6 pathway for HR^+ and $HER2^-$ breast cancer.[15] In some clinical trials, CDK4/6 inhibitors combined with endocrine therapy significantly improved the progression-free survival and overall survival of patients.[16] In a multicenter real-world data analysis, 448 patients with $HR^+/HER2^-$ advanced breast cancer received CDK4/6 inhibitor combined with endocrine therapy, and the median PFS was 17 months, indicating that this treatment regimen plays an important role in blocking the CDK4/6 pathway and controlling tumor progression.[17] CDK4/6 inhibitors may also affect tumor growth and metastasis by regulating mechanisms such as the tumor microenvironment.

In the univariate analysis, ER level, liver metastasis, stomatitis, and number of treatment lines were significantly associated with prognosis. However, in the multivariate model, only ER level emerged as an independent protective factor, while liver metastasis showed a trend toward being a risk factor without reaching statistical significance ($P = 0.393$). Bone metastasis, which was not significant in univariate analysis, was further confirmed as non-significant in the multivariate model ($P = 0.393$). These findings highlight ER level as a robust predictor of treatment response in patients receiving CDK4/6i combined with ET.

Beyond confirming the survival benefit of the combination therapy, our analysis sought to identify factors associated with prognosis in this treatment context. The COX regression analyses yielded insights with potential clinical relevance. Most notably, we identified ER expression level as an independent protective factor for PFS in the multivariate model. This reinforces the fundamental role of ER as the primary therapeutic target and suggests that quantitative ER assessment might offer finer prognostic stratification than mere positivity status in patients receiving CDK4/6i-based regimens, a nuance that merits further investigation in larger cohorts.[18] Conversely, liver metastasis emerged as a significant risk factor in univariate analysis. Although it was attenuated in the multivariate model, possibly due to sample size or correlation with other variables, its strong univariate association underscores the aggressive nature of breast cancer with hepatic involvement. This finding highlights a subgroup of patients—those with liver metastases—who may experience poorer outcomes and for whom more vigilant monitoring or intensified treatment strategies could be considered.

The common adverse reactions of CDK4/6i (such as fatigue and stomatitis) are mostly grade I–II. Consistent with previous studies, they can be effectively controlled through dose adjustment or supportive treatment, indicating that the security of combined treatment is controllable. Stomatitis was shown as a prognostic protective factor in the univariate analysis, which might be related to the sensitivity of patients to treatment reflected by stomatitis. Common adverse reactions of CDK4/6 inhibitors include hematological and non-hematological toxicities. In terms of hematological toxicity, neutropenia is a relatively prominent adverse reaction, and the incidence varies among different inhibitors.[19] In some studies, the incidence of neutropenia was relatively high during the treatment with palbociclib and ribociclib. An analysis of the FDA's adverse event reporting system found that palbociclib showed a higher risk signal in terms of hematological toxicity.[20] Non-hematological toxicities include diarrhea, fatigue, nausea, vomiting, hepatotoxicity, etc. Take diarrhea as an example. The incidence of diarrhea is relatively high when treated with abemaciclib. In one study, diarrhea was more common among patients treated with abemaciclib.[21] For these adverse reactions, clinical management usually includes dose adjustment, supportive treatment, etc. When neutropenia occurs, the drug dose can be appropriately reduced or the administration delayed according to the severity, and supportive treatments such as granulocyte colony-stimulating factor can be given. For diarrhea, antidiarrheal drugs can be used for symptomatic treatment.

This study was a retrospective single-center study, with limitations such as unbalanced baseline treatment line numbers and small sample sizes, and the analysis of biomarkers (such as Ki-67 and PIK3CA mutations) was not included. Prospective studies are needed in the future to verify the correlation between ER levels and the efficacy of CDK4/6i, and to explore individualized treatment strategies guided by molecular markers. Nevertheless, the results of this study support CDK4/6i

combined with ET as the preferred regimen for HR^+HER2^- advanced breast cancer, especially for patients with high ER expression and no extensive liver metastasis.

Conclusions

This real-world study confirms the significant clinical benefit and manageable security profile of CDK4/6 inhibitor combined with endocrine therapy in patients with $HR^+/HER2^-$ advanced breast cancer. Importantly, our analysis extends beyond efficacy validation by identifying the level of ER expression as a key independent protective factor and underscoring the particularly poor prognosis associated with liver metastasis in this treatment setting. These findings support the use of combined therapy while also pointing to potential biomarkers for risk stratification that could inform more individualized patient management.

Ethics Approval and Consent to Participate

The study was approved by the General Hospital of Ningxia Medical University and all the subjects provided their written informed consent before participation. All methods were performed in accordance with the relevant guidelines and regulations.

Author Contributions

Yan Wang and Dongmei Chen should be considered co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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