Editorial

CDK4/6 inhibitors combined with fulvestrant for HR$^+$/HER2$^-$ advanced breast cancer

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Introduction

In recent years, the cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors combined with endocrine therapy has become the major breakthrough therapy for patients with hormone receptor (HR)$^+$/human epithelial receptor 2 (HER2)$^-$ advanced breast cancer (ABC), and has been shown to significantly prolong the progression-free survival (PFS) of patients compared to endocrine monotherapy (1). Several products have been approved for 1st- and 2nd-line therapy. In 2021, a key phase-III clinical study of CDK4/6 inhibitors released its overall survival (OS) results, median OS was 53.7 months in ribociclib-fulvestrant group *vs.* 41.5 months in placebo-fulvestrant group (2). The treatment goal for ABC is to improve the OS of patients. The comprehensive evaluation of PFS, OS, and quality of life enables more precise clinical treatment decision making.

In 2021, the Chinese originator CDK4/6 inhibitor dalpiciclib was indicated for the 2nd-line treatment of patients with HR$^+$/HER2$^-$ in China (3), and thus the accessibility of CDK4/6 inhibitors was greatly improved for Chinese breast cancer patients, enriching their treatment options. As no studies have been conducted on the use of different CDK4/6 inhibitors in treating ABC, there are both similarities and differences in the population characteristics, results, and benefits of the different studies, especially in studies involving CDK4/6 inhibitors combined with fulvestrant. We reviewed classical studies on the combination of different CDK4/6 inhibitors and fulvestrant, summarizing the limitations of the study designs, and discussing the clinical value and significance of the study results, to guide the clinical application of CDK4/6 inhibitors in Chinese patients with HR$^+$/HER2$^-$ ABC.

CDK4/6 inhibitor combined with fulvestrant for 1st-line therapy

CDK4/6 inhibitors plus aromatase inhibitors (AIs) or fulvestrant produce consistent benefits in 1st-line treatments. In the MONALEESA-3 study, 50% of the patients had 1st-line HR$^+$/HER2$^-$ ABC (4). An updated OS exploratory analysis was conducted after a median follow-up period of 56.3 months (2). The median OS in the ribociclib group and placebo group was 53.7 and 41.5 months, respectively [hazard ratio (HR) =0.73, 95% confidence interval (CI): 0.59–0.90] (2). With an extended follow-up period of >4 years, the ribociclib group continued to demonstrate a clinically relevant OS benefit beyond 1 year compared to that of the placebo group. For patients who received ribociclib in the 1st-line setting, 60% of patients in the ribociclib group lived longer than median follow-up, the median OS was 51.8 months in the placebo group (HR =0.64, 95% CI: 0.46–0.88). A consistent OS benefit was found across most subgroups, including among patients who were harder to treat. The benefits were observed regardless of the therapy setting, particularly in 1st-line treatment (HR =0.63, 95% CI: 0.47–0.84) (2). In the PARSIFAL trial (5), the median PFS was 27.9 months

in the palbociclib-fulvestrant group and 32.8 months in the palbociclib-letrozole group. The results were consistent between the 2 groups. The 1st-line subgroup results confirmed that the CDK4/6 inhibitor in combination with fulvestrant had a significant PFS advantage over fulvestrant alone (5). The other 2 kinds of CDK4/6 inhibitors have not been compared with each other to examine their efficacy in combination with AI or fulvestrant.

CDK4/6 inhibitor combined with fulvestrant for 2nd-line therapy

Palbociclib, ribociclib, abemaciclib, and dalpiciclib combined with fulvestrant showed similar effectiveness in the 2nd-line treatment of different patients. In the PALOMA-3 study (6), the PFS of patients receiving palbociclib-fulvestrant as a 2nd-line treatment was significantly prolonged compared to that of patients receiving placebo-fulvestrant as a 2nd-line treatment (median 9.5 *vs.* 5.4 months, HR =0.55, 95% CI: 0.32–0.92). The PALOMA-3 trial involved more patients and more post-line patients, of whom 54% received >3rd-line treatment and 33% received chemotherapy (6). At the American Society of Clinical Oncology (ASCO) Conference in 2021, an update of the PALOMA-3b trial revealed that the palbociclib-fulvestrant treatment tended to prolong the OS of patients compared to the placebo-fulvestrant treatment (median 34.8 *vs.* 28.0 months, absolute benefit 6.8 months) (7). The subgroup analysis showed that palbociclib-letrozole significantly prolonged the OS of patients with secondary resistance and the OS of patients who had not received advanced chemotherapy, with an absolute benefit of 10.2 and 9.6 months, respectively (6,7). In the other CDK4/6 inhibitor trials (with the exception of dalpiciclib), patients who had received advanced chemotherapy were not allowed to be enrolled. The interference of these different baseline characteristic on the research results is worth considering.

The MONARCH-2 study showed that patients who received abemaciclib plus fulvestrant had a significantly prolonged PFS compared to those who received placebo-fulvestrant as a 2nd-line therapy (with a median of 17.39 *vs.* 7.36 months, respectively; HR =0.478, 95% CI: 0.357–0.639) (8). At a median follow-up time of 47.7 months, the OS of the abemaciclib plus fulvestrant group was statistically longer than that of the placebo plus fulvestrant group (HR =0.76, 95% CI: 0.61–0.95) (9). The median OS of the abemaciclib group and placebo group was 46.7 and 37.3 months, respectively (9). Despite the statistical certainty of these interim results, the further determination of OS and other exploratory efficacy endpoints still have important clinical significance. Such analyses will be performed in the final OS analysis of the MONARCH2 trial.

In the MonaleesA-3 trial, PFS was significantly increased among patients receiving ribociclib plus fulvestrant as a 2nd- or post-line treatment (HR =0.565, 95% CI: 0.428–0.744) (4). An updated OS exploratory analysis was conducted after a median follow-up period of 56.3 months (2). The median OS was 53.7 months in the ribociclib group and 41.5 months in the placebo group (HR =0.73, 95% CI: 0.59–0.90). In the 2nd-line treatment, the median OS was 39.7 and 33.7 months in the ribociclib-containing group and the placebo-containing group, respectively (HR =0.78, 95% CI: 0.59–1.04) (2).

The DAWNA-1 study (3) enrolled Chinese patients with HR^+HER2^- ABC, of whom 44% were premenopausal or perimenopausal. The proportion of patients who received chemotherapy at an advanced stage was 27%, and the proportion of patients with visceral metastasis was 58.9%. The primary endpoint of PFS in the dalpiciclib-fulvestrant group was significantly longer than that in the placebo-fulvestrant group. The PFS was 15.7 months [95% CI: 11.1 months–not reached (NR)] in dalpiciclib-fulvestrant group and 7.2 months (95% CI: 5.6–9.2 months) in placebo-fulvestrant group, the HR value was 0.42 (95% CI: 0.31–0.58), the median PFS increased by 8.5 months, and the HR value was the lowest in previous CDK4/6 inhibitor studies (3). The DAWNA-1 study did not include patients with primary endocrine therapy resistance. Thus, the efficacy of dalpiciclib in patients with primary endocrine therapy resistance needs to be further explored. Further, the long-term outcomes are not yet clear and thus long-term follow-up is needed. Due to the special piperidine structure of dalpiciclib, the incidence and severity of the hepatotoxicity of dalpiciclib was lower than that of several other CDK4/6 inhibitors in Chinese populations (3).

CDK4/6 inhibitors combined with fulvestrant *vs.* chemotherapy

Young-PEARL (10) and PEARL (11) compared the treatment of $HR^+/HER2^-$ ABC with CDK4/6 inhibitor plus endocrine and capecitabine monotherapy, but found inconsistent results. The Young-PEARL phase II study was the first to compare CDK4/6 inhibitor plus endocrine

therapy to chemotherapy in premenopausal HR$^+$/HER2$^-$ ABC patients. The median PFS was 20.1 months in the Palbociclib plus endocrine therapy group, but only 14.4 months in the capecitabine group (HR =0.66, 95% Cl: 0.44–0.99; P=0.0469) (10). PEARL was a multicenter, randomized phase-III study, in which patients with AI-resistant ABC were enrolled in 2 cohorts (11). The patients were randomly assigned to palbociclib-exemestane or capecitabine using a 1:1 ratio in cohort 1. However, no statistical advantage was found between palbociclib-exemestane and capecitabine in terms of PFS and OS. The most reasonable explanation for the inconsistencies in these results is that the population characteristics of the cohorts in the 2 trials differed. The prognosis of the PEARL patients was worse than that of Young-PEARL patients. Indeed, >80% of PEARL patients were treated with multiple lines of therapy, and all the patients received 1 or more lines of endocrine therapy, 70% of the patients had AI-resistance, and 28.8% of patients had fulvestrant-resistance. As a result, the therapeutic effects of the endocrine therapy were significantly reduced, which led to the negative results. The Young-PEARL and PEARL studies also suggested that patients treated with a CDK4/6 inhibitor combined with endocrine therapy benefit more from front-line treatment, and chemotherapy should only be considered after disease progression.

Conclusions

In summary, these trials confirmed the prolonged and consistent benefit of CDK4/6 inhibitors plus fulvestrant in the treatment of HR$^+$/HER2$^-$ ABC. The findings of the PALOMA-3, MONARCH-2, MONALEESA-3, and DAWNA-1 trials in relation to treatment outcomes is worth considering due to the differences in the enrolled populations. However, in terms of efficacy, the comparison data of the different agents is insufficient to inform decisions about the selection of available CDK4/6 inhibitors. Thus, real-world research needs to be conducted to guide the clinical application of CDK4/6 inhibitors across different populations. CDK4/6 inhibitors plus endocrine therapy are used in front-line therapy, and chemotherapy should be considered after treatment progress to bring greater benefits to patients. Effective treatment methods and efficacy predictors are still lacking for patients who develop a resistance to CDK4/6 inhibitors. The effective therapy of CDK4/6 inhibitors resistance is currently under exploration.

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