Chemotherapy-free neoadjuvant strategy in HR+/HER2- early breast cancer: CDK4/6 inhibitors plus endocrine therapy show comparable efficacy to chemotherapy-sequenced approach

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Introduction

- Hormone receptor-positive, human epidermal growth factor 2-negative (HR+/HER2-) breast cancer constitutes 69% of all breast cancers[1]. In China, 68% of HR+/HER2– early breast cancer cases have stage II-III disease[2]. Neoadjuvant therapy aims to downstage tumors, shrink tumors, increase breast-conserving surgery rates, and improve the prognosis of patients with HR+/HER2- early breast cancer.
- Neoadjuvant chemotherapy has historically been the standard treatment for HR+/HER2– early breast cancer; however, its pathological complete response (pCR) rates remain low (7.5%–16.2%)[3]. Furthermore, chemotherapy-related toxicities may compromise treatment adherence and quality of life in HR+/HER2– early breast cancer patients.
- In recent years, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors with promising efficacy have reshaped the therapeutic landscape for adjuvant treatment of HR+/HER2- breast cancer[4]. In the CORALLEEN phase 2 trial, neoadjuvant ribociclib plus letrozole shows comparable efficacy to neoadjuvant chemotherapy but fewer side effects in patients with HR+/HER2– early stage breast cancer[5]. Similarly, the WSG-ADAPTcycle phase 3 trial reports that neoadjuvant ribociclib plus endocrine therapy yields similar pCR compared with chemotherapy in intermediate-risk HR+/HER2- early breast cancer[6]. Despite these findings, the role of chemotherapy omission in the neoadjuvant setting remains controversial.
- This real-world study evaluated the objective response rate (ORR) and safety of neoadjuvant CDK4/6 inhibitors plus endocrine therapy versus neoadjuvant chemotherapy followed by endocrine therapy plus CDK4/6 inhibitors, and explored endocrine-sensitivity biomarkers to guide chemotherapy-sparing strategies.

Methods

- This study included 91 patients diagnosed with HR+/HER2- early breast cancer at 11 tertiary hospitals in China. Considering that age >70 years may influence prognosis and chemotherapy decisions, 63 patients aged ≥ 18 and ≤70 years with complete treatment and follow-up data were included in the analysis. Among them, 38 patients received endocrine therapy plus CDK4/6 inhibitors (ribociclib [n=17], abemaciclib [n=13], dalpiciclib [n=7], palbociclib [n=1]), and 25 patients received chemotherapy followed by endocrine therapy plus CDK4/6 inhibitors.
- ORR was defined as complete/partial radiologic response according to RECIST 1.1 criteria. For statistical analysis, the Mann-Whitney U test was used to analyze ranked data. The χ2 test or Fisher's exact test was used to analyze categorical data. Logistic regression analysis was performed to identify significant factors for treatment response. All tests were two sided with significance level set at 0.05. All data cleaning and analysis were conducted using R statistical software (Version 4.5.0).

Results

- Baseline clinical characteristics were well balanced between the two treatment groups (all P>0.05, **Table 1**).

Table 1. Baseline clinical characteristics

Characteristic	All patients (n=63)	endocrine therapy plus CDK4/6 inhibitors (n=38)	chemotherapy followed by endocrine therapy plus CDK4/6 inhibitors (n=25)	P value
Age, median (minimum, maximum)	55 (33-70)	55 (35-70)	55 (33-68)	0.201
Menopausal status, n (%)				0.536
Premenopausal	26 (37)	14 (31)	12 (48)	
Postmenopausa	37 (63)	24 (69)	13 (52)	
T stage, n (%)				0.702
T0-1	8 (11)	4 (9)	4 (16)	
T2-4	55 (89)	34 (91)	21 (84)	
Nodal status, n (%)				0.759
T0-1	33 (53)	21 (56)	12 (48)	
N2-3	30 (47)	17 (44)	13 (52)	
Histologic SBR grade, n (%)				0.445
G1-2	45 (83)	25 (78)	20 (91)	
G3	8 (17)	6 (22)	2 (9)	
Baseline Ki67 levels, median (minimum, maximum)	25 (5-80)	20 (5-70)	30 (10-80)	0.077
Post-treatment Ki67 levels, median (minimum, maximum)	10 (0-70)	10 (0-70)	10 (1-40)	0.992
Change in Ki67 levels	-8 (-75-30)	-8 (-29-30)	-9 (-75-10)	0.308
ER expression	90 (20-100)	90 (40-100)	90 (20-90)	0.102
PR expression	70 (0-99)	75 (0-99)	70 (0-90)	0.326
HER2 expression				0.605
0-1	39 (60)	25 (62)	14 (56)	
2-3	24 (40)	13 (38)	11 (44)	

Note: SBR=Scarff-Bloom-Richardson, ER=estrogen receptor; PR= progesterone receptor.

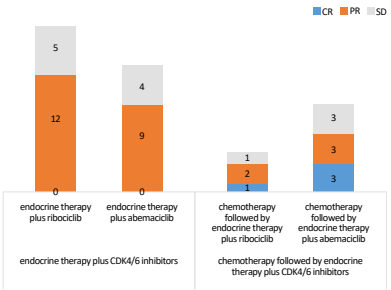
- Regardless of treatment regimen, the overall ORR was 62% (**Table 2**). The ORR was comparable between the endocrine therapy plus CDK4/6 inhibitors and chemotherapy followed by endocrine therapy plus CDK4/6 inhibitors groups (68% versus 52%, OR [odds ratio]: 0.41, 95% CI: 0.10-1.56, P=0.200).

Table 2. ORR analyses

	ORR	Clinical response (CASE)	total (CASE)
All patients	62%	39	63
Patients treated with endocrine therapy plus CDK4/6 inhibitors	68%	26	38
Ki67≤20	73%	16	22
Ki67>20	63%	10	16
Patients treated with chemotherapy followed by endocrine therapy plus CDK4/6 inhibitors	52%	13	25
Ki67≤20	50%	4	8
Ki67>20	53%	9	17

- Ki-67 index is an independent predictor of recurrence risk in breast cancer. According to guidelines for breast cancer diagnosis and treatment by China Anti-cancer Association (2024 edition), Ki-67 ≤20% indicates low postoperative recurrence risk[7]. Therefore, stratified analysis was performed based on Ki67≤20% and Ki67>20%. In the Ki67>20% subgroup, the ORR was 63% in endocrine therapy plus CDK4/6 inhibitors group and 53% in chemotherapy followed by endocrine therapy plus CDK4/6 inhibitors group, without statistically significant difference (OR: 0.91, 95% CI: 0.64 - 1.29, P=0.683). In the Ki67≤20% subgroup, the ORR was similar between two groups (endocrine therapy plus CDK4/6 inhibitors group versus endocrine therapy plus CDK4/6 inhibitors group: 73% versus 50%; OR: 0.797, 95% CI: 0.542-1.172, P=0.0348).
- A total of 38 patients received endocrine therapy plus CDK4/6 inhibitors (abemaciclib [n=13], ribociclib [n=17], dalpiciclib [n=4], palbociclib [n=1], unknown [n=3]). Additionally, 25 patients received chemotherapy followed by endocrine therapy plus CDK4/6 inhibitors (abemaciclib [n=9], ribociclib [n=4], dalpiciclib [n=11], palbociclib [n=1]). To ensure the consistency of follow-up data, ORR was analyzed only for patients received ribociclib or abemaciclib.
- As shown in **Figure1**, in the endocrine therapy plus ribociclib group, 12 patients achieved partial response (PR), 5 had stable disease (SD). In the endocrine therapy plus abemaciclib group, 9 patients achieved PR, 4 had SD. In the chemotherapy-sequenced endocrine therapy plus ribociclib group, 1 patient achieved complete response (CR), 2 had PR, and 1 achieved SD. In the chemotherapy-sequenced ET plus abemaciclib group, 3 patients achieved CR, 3 achieved PR, and 3 had SD.

Figure 1. The efficacy analyses of treatment groups



- Among chemotherapy- naïve patients receiving ribociclib or abemaciclib, baseline characteristics were similar (all P>0.05, **Table 3**).

Table 3. Baselines patients' characteristics in ribociclib and abemaciclib groups

Characteristics	abemaciclib (n=13)	ribociclib (n=17)	P value
Age, median (minimum, maximum)	53 (41-70)	50 (36-70)	0.544
Menopausal status, n (%)			1.000
Premenopausal	5 (38)	7 (42)	
Postmenopausal	8 (62)	10 (58)	
T stage, n (%)			1.000
T0-1	1 (8)	2 (12)	
T2-4	12 (92)	15 (88)	
Nodal status, n (%)			0.260
N0-1	10 (77)	9 (50)	
N2-3	3 (23)	9 (50)	
Histologic SBR grade, n (%)			
G1-2	12 (92)	7 (70)	0.165
G3	1 (8)	3 (30)	
Baseline Ki67 levels, median (minimum, maximum)	18 (8-50)	20 (2-70)	0.832
Post-treatment Ki67 levels, median (minimum, maximum)	10 (4-15)	10 (2-60)	0.897
Ki67 change	-7 (-10-0)	-5 (-26-0)	0.835
ER expression	90 (70-99)	90 (60-99)	0.654
PR expression	80 (30-99)	80 (40-99)	1.000
HER2 expression			0.440
0-1	10 (77)	10 (59)	
2-3	3 (23)	7 (41)	

- In chemotherapy-naïve patients, ORR was 71% with ribociclib and 69% with abemaciclib (OR: 1.07, 95% CI: 0.21–5.21, P=0.936), with PR observed in 9 and 12 patients in ribociclib and abemaciclib groups, respectively (**Table 4**).

Table 4. The treatment response of ribociclib and abemaciclib group

Characteristics	All patients	PR, N	OR (95% CI)	P value
Treatments				
Abemaciclib	13	9	1.00	
Ribociclib	17	12	1.07 (0.21-5.21)	0.936

Limitations

- As a retrospective real-world analysis, the study is subject to potential bias due to collection timeframe, non-randomization, and incomplete follow-up. Further follow-up and expanded sample size are warranted.

Conclusions

- In HR+/HER2- early breast cancer patients aged 18–70 years, real-world evidence suggests that neoadjuvant endocrine therapy plus CDK4/6 inhibitor achieves short-term ORR comparable to chemotherapy followed by endocrine therapy plus CDK4/6 inhibitors. These findings support the feasibility of chemotherapy-free neoadjuvant approaches in clinically selected HR+/HER2- breast cancer patients, with potential to maintain efficacy while mitigating chemotherapy-related toxicity and preserving quality of life.

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