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Outcomes of Everolimus Plus Endocrine Therapy Following CDK4/6 Inhibitor Therapy for Metastatic Hormone Receptor-Positive Breast Cancer

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ABSTRACT Objective: This study investigated the effectiveness and safety of everolimus plus endocrine therapy in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer (MBC) after failed cyclin-dependent kinase 4/6 (CDK4/6) inhibitor therapy in a real-world clinical setting. **Material and Methods:** This was a single-center retrospective cohort study. Patients with HR+/HER2- MBC who underwent everolimus plus endocrine therapy after prior progression with combination of a CDK4/6 inhibitor and a hormonal therapy were included. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method, and parameters associated with PFS were assessed by Cox regression analysis. **Results:** A total of 44 patients were included. The median PFS was 4.1 months [95% confidence interval (CI), 2.8-5.4] and the median OS was 16 months (95% CI, 8.8-23.2). Liver metastasis [hazard ratio (HR), 2.28; 95% CI, 1.09-4.78; p=0.029] and pleural or peritoneal metastases (HR, 3.23; 95% CI, 1.46-7.14; p=0.004) were associated with poor PFS. Multivariate Cox regression analysis after covariate adjustment for age and histology revealed that liver (HR, 2.21; 95% CI, 1.04-4.69; p=0.038) and pleural or peritoneal metastases (HR, 3.01; 95% CI, 1.35-6.70; p=0.007) were significantly associated with increased risk of PFS events. **Conclusion:** Everolimus plus endocrine therapy has a moderate effect on PFS in patients with MBC who had previously received a CDK4/6 inhibitor and hormonal agent combination therapy. The effect is more pronounced in patients without liver or pleural/peritoneal metastases.

Keywords: Breast neoplasms; everolimus; cyclin-dependent kinase; aromatase inhibitors

Breast cancer is the most common cancer among women worldwide, and hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer represents its largest subgroup, constituting approximately 70% of cases.[1,2] Improved treatments and earlier detection have contributed to increased survival of patients with both non-metastatic and metastatic breast cancers (MBCs) in recent decades.[3,4] However, MBC remains an incurable condition.

Endocrine therapies targeting the estrogen pathway, including tamoxifen, aromatase inhibitors, and more recently fulvestrant, have been become the cornerstone of HR+/HER2- MBC treatment.[5] In recent decades, HR+/HER2- MBC treatment has evolved remarkably with the introduction of novel therapeutic agents that enhance the efficacies of endocrine therapies. Everolimus, a mammalian target of rapamycin inhibitor, has emerged as a valuable drug to counter endocrine resistance. The combination ther-

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apy with everolimus and exemestane, an aromatase inhibitor, has been shown to improve progression-free survival (PFS) and response rate in postmenopausal patients with HR+/HER2- MBC who experienced disease progression after treatment with nonsteroidal aromatase inhibitors.[6] In 2012, everolimus was approved by the United States Food and Drug Administration, and since then, it has been used in combination with exemestane as a standard second-line treatment for HR+/HER2- breast cancer in postmenopausal women after failed first-line letrozole or anastrozole treatment.[7] Recently, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, including palbociclib, ribociclib, and abemaciclib, have been shown to markedly improve clinical outcomes in patients with HR+/HER2- MBC when used in combination with first line endocrine therapy.[8] CDK4/6 inhibitor plus endocrine therapy has become the standard first-line treatment for HR+/HER2-MBC.[9]

However, there is limited evidence on the optimal treatment strategy after failed CDK4/6 inhibitor therapy. Since the efficacy of everolimus was evaluated prior to the introduction of CDK4/6 inhibitors, it remains unclear whether everolimus can confer similar clinical benefits in patients with disease progression following failed CDK4/6 inhibitor plus endocrine therapy. In this study, we evaluated the effectiveness and safety of everolimus plus endocrine therapy for HR+/HER2- MBC with disease progression after first-line treatment including CDK4/6 inhibitors. Further, we assessed the clinical parameters associated with treatment outcomes of everolimus therapy.

MATERIAL AND METHODS

STUDY DESIGN AND SETTING

This retrospective cohort study was conducted at the medical oncology clinic of Bahrain Oncology Center, a comprehensive cancer center serving the majority of patients diagnosed with solid organ malignancies in the Kingdom of Bahrain. This study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board of King Hamad University Hospital (date: November 27, 2022, reference: 22-555).

PATIENTS

The study population was identified through a review of electronic medical and pharmacy records of patients treated in the medical oncology clinic from January 2018 to June 2023. This study included women aged over 18 years diagnosed with biopsy-proven HR+/HER2- MBC who had previously been treated with CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) plus endocrine therapy (letrozole, anastrozole, exemestane, tamoxifen, or fulvestrant), experienced radiological progression of breast cancer, and subsequently received everolimus plus endocrine therapy.

Clinical data were extracted from the electronic medical record system of the hospital. Data, including age, tumor characteristics, initial disease stage, previous treatments, duration of CDK4/6 inhibitor treatment, metastatic sites before starting on everolimus therapy, everolimus treatment duration, reason for everolimus discontinuation, survival status, and survival duration, were recorded. Safety data were obtained from records of clinic visits, emergency visits, admission notes, and laboratory results. Data on the following adverse events were collected: stomatitis, pneumonitis, anemia, leukopenia, neutropenia, and elevated alanine and aspartate transaminase levels.

STATISTICAL ANALYSIS

Categorical variables were summarized as frequencies and percentages. Continuous variables were summarized as medians and interquartile ranges (IQRs). PFS and overall survival (OS) estimates were calculated using the Kaplan-Meier method and represented as medians and 95% confidence intervals (CIs). PFS was measured from the date of initiation of everolimus to the date of disease progression, determined by imaging results, or date of death, whichever occurred first. OS was measured from the date of initiation of everolimus to the date of death. Cases were censored at the date of last contact, if the event of interest did not occur. Survival estimates were compared between groups using log-rank test. Cox regression analysis was performed to assess the clinical parameters associated with PFS. The statistical analyses were performed using PASW statistics software version 18.0 (SPSS Inc., USA, 2009).

RESULTS

PATIENTS AND TREATMENT

A total of 44 patients were included in this study. Baseline characteristics of the patients are provided in Table 1. The median age was 58.1 years (IQR: 49.8-65.5 years), and 75% of the patients were postmenopausal. Invasive ductal carcinoma (IDC) was the most common histological subtype (66%), followed by lobular carcinoma (27%). Histological grades in the study population and the corresponding numbers of patients were as follows: Grade 1 in one patient (2%), 2 in 24 (55%), 3 in 10 (23%), and unknown in nine patients. At the time of initial diagnosis, 25 patients (57%) had metastatic and 19 (43%) had localized disease. Adjuvant chemotherapy, radiotherapy, and endocrine therapy were administered to 17 (39%), 16 (36%), and 19 (43%) patients, respectively. At least one visceral metastasis was present in 25 patients (57%). Moreover, 12 (27%), 11 (25%), 10 (23%), and two (4.5%) patients had liver, lung, pleural or peritoneal, and brain metastases, respectively, and nine patients (20.5%) had bone-only disease. The median duration of CDK4/6 inhibitor therapy was 13.2 months (IQR: 7.5-20.9). The median duration of metastatic disease before starting on everolimus therapy was 23.7 months (IQR: 15.9-41.1). The numbers of previous treatment lines, including adjuvant treatments, were one in 11 (25%), two in 8 (18%), and three or more in 25 (57%) patients.

TABLE 1: Baseline characteristics.

Parameters		Results* (n=44)
Age (years)	Median (IQR)	58.1 (49.8-65.5)
Menopausal status	Premenopausal	11 (25%)
	Postmenopausal	33 (75%)
Histological subtype	IDC	29 (66%)
	ILC	12 (27%)
	Other	3 (7%)
Grade	1	1 (2%)
	2	24 (55%)
	3	10 (23%)
	Unknown	9 (20%)
Stage at diagnosis	Localized	19 (43%)
	Metastatic	25 (57%)
Prior treatments	Neoadjuvant or adjuvant chemotherapy	17 (39%)
	Adjuvant radiotherapy	16 (36%)
	Adjuvant hormonal treatment	19 (43%)
	Chemotherapy for MBC	14 (32%)
Number of metastatic sites	1	11 (25%)
	2	15 (34%)
	3 or more	18 (41%)
Metastatic sites	Visceral metastasis	25 (57%)
	Liver metastasis	12 (27%)
	Lung metastasis	11 (25%)
	Pleura or peritoneum	10 (23%)
	Bone-only	9 (20.5%)
Duration on CDKi (months)	Median (IQR)	13.2 (7.5-20.9)
Metastatic disease duration before everolimus (months)	Median (IQR)	23.7 (15.9-41.1)
No. of prior treatment lines**	1	11 (25%)
	2	8 (18%)
	3 or more	25 (57%)

*The results are presented as count (percentage) or median (interquartile range). **Prior treatment lines include the adjuvant setting and treatments for metastatic disease. CDKi, cyclin-dependent kinase 4/6 inhibitor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IQR, interquartile range; MBC, metastatic breast cancer.

The median treatment duration with everolimus was 4.0 months (IQR: 2.7-6.9). The concurrent endocrine agent was exemestane in 37 patients (84%), fulvestrant in 5 (11%), and tamoxifen in 2 (5%). Everolimus was discontinued due to disease progression, toxicity or intolerance, and death in 33 (75%), 6 (14%), and 1 (2%) patients, respectively. At the time of data cutoff, three patients were undergoing everolimus therapy, and one was lost to follow-up.

EFFECTIVENESS

The median follow-up duration was 11 months (95% CI, 5.2-16.8). Overall, 39 patients (89%) experienced a PFS event, and the median PFS was 4.1 months (95% CI, 2.8-5.4). The median OS was 16 months (95% CI, 8.8-23.2) after 19 OS events (Figure 1).

Univariate Cox proportional hazards model was used to assess the associations between various clinical parameters and PFS (Table 2). Liver [hazard ratio (HR), 2.28; 95% CI, 1.09-4.78; p=0.029] and pleural or peritoneal metastases (HR, 3.23; 95% CI, 1.46-7.14; p=0.004) were associated with poor PFS. Age, number of metastatic sites, duration of prior CDK4/6 inhibitor therapy, metastatic disease duration before starting on everolimus, and number of treatment lines

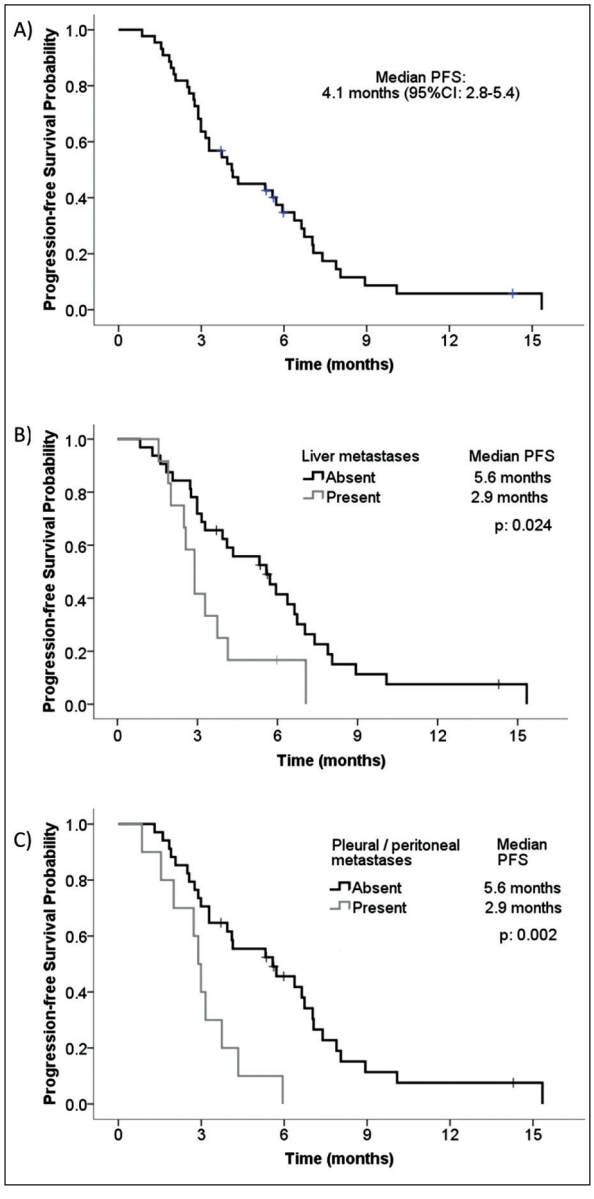

FIGURE 1: Kaplan-Meier Curves of Progression-Free Survival (PFS) in all patients **(A)**, categorized by liver metastasis **(B)**, and pleural/peritoneal metastasis statuses **(C)**. CI, confidence interval; PFS, progression-free survival.

before starting on everolimus were not associated with PFS. Multivariate Cox regression analysis after adjusting covariates for age and histology (IDC vs non-IDC), presence of liver (HR, 2.21; 95% CI, 1.04-4.69; p=0.038), and pleural or peritoneal metastases (HR, 3.01; 95% CI, 1.35-6.70; p=0.007) were significantly associated with increased risk of PFS events.

SAFETY

Anemia, leucopenia, and neutropenia were observed in 45%, 50%, and 34% of the patients, respectively. Grade 3 or 4 anemia, leucopenia, and neutropenia were observed in 11%, 2%, and 7% of the patients, respectively. Elevated alanine and aspartate transaminase levels were reported in 20% and 16% of the patients, respectively. Stomatitis, diarrhea, and pneumonitis were reported in 18%, 9%, and 9% of the patients, respectively. No Grade 4 pneumonitis was observed (Table 3). Dose reduction was required in 14 (32%) patients. Emergency room and hospital admissions were required in 7 (16%) and 8 (18%) cases, respectively. No treatment-related deaths were reported.

DISCUSSION

This study showed that everolimus plus endocrine therapy has moderate effectiveness in patients with HR+/HER2- MBC who underwent prior treatment with CDK4/6 inhibitors. The BOLERO-2 trial demonstrated that combination treatment with everolimus and exemestane improved PFS in patients with HR+/HER2- MBC who were previously treated with nonsteroidal aromatase inhibitors.[6] In the final analysis of this trial, the PFS was 7.2 months in the everolimus plus exemestane arm and 3.2 months in the exemestane only arm; OS was similar in both arms.[10,11] In our study, the median PFS was 4.1 months, which is shorter than that observed in the BOLERO-2 trial. Nevertheless, our study cohort exhibited similarities to that of the BOLERO-2 trial across several key parameters. The median age was 58 years in our study, which is slightly lower than that in the BOLERO-2 trial (62 years). Visceral metastasis was found in 57% of the patients in our study, closely mirroring the findings of the BOLERO-2 trial (56%). Moreover, 57% of patients in our study received three or more lines of treatment, consistent with the findings of the BOLERO-2 trial (54%). The main difference between the cohorts is prior exposure to CDK4/6 inhibitors, which may be a key factor contributing to the shorter PFS in our study.

There is a paucity of retrospective study-based data on the efficacy of everolimus plus endocrine therapy after failed CDK4/6 inhibitor therapy. A previous retrospective study on the effectiveness of everolimus plus exemestane in patients with prior

TABLE 2: Cox regression analysis for progression-free survival.

Parameters		HR (95%CI)	p value
Univariable analysis			
Age	Cont.	1.01 (0.98-1.04)	0.54
Histology	IDC (Ref) vs. non-IDC	1.83 (0.94-3.58)	0.075
Visceral metastasis	No (Ref) vs. Yes	1.55 (0.81-2.96)	0.19
Liver metastasis	No (Ref) vs. Yes	2.28 (1.09-4.78)	0.029
Lung metastasis	No (Ref) vs. Yes	0.49 (0.22-1.08)	0.077
Peritoneal/pleural metastasis	No (Ref) vs. Yes	3.23 (1.46-7.14)	0.004
Bone-limited	No (Ref) vs. Yes	0.43 (0.18-1.04)	0.062
No. of metastatic sites	≤2 (Ref) vs. >2	1.41 (0.73-2.72)	0.301
CDKi duration	Cont.	1.00 (0.97-1.03)	0.99
Metastatic disease duration before everolimus	Cont.	1.00 (0.98-1.02)	0.90
No. treatment lines before everolimus	1 or 2 (Ref) vs. 3 or more	1.35 (0.69-2.64)	0.38
Covariate-adjusted*			
Liver metastasis	No (Ref) vs. Yes	2.21 (1.04-4.69)	0.038
Lung metastasis	No (Ref) vs. Yes	0.45 (0.19-1.08)	0.075
Peritoneal/pleural metastasis	No (Ref) vs. Yes	3.01 (1.35-6.70)	0.007
Bone-limited	No (Ref) vs. Yes	0.45 (0.19-1.09)	0.076

*Adjusted for age and histology (IDC vs non-IDC). CDKi, cyclin-dependent kinase inhibitor; Cont, continuous variable; HR, hazard ratio; IDC, invasive ductal carcinoma; Ref, reference.

TABLE 3: Treatment-related adverse events.

Parameters	Any grade	Grade 3-4
Anemia	20 (45%)	5 (11%)
Leucopenia	22 (50%)	1 (2%)
Neutropenia	15 (34%)	3 (7%)
Increased ALT	9 (20%)	1 (2%)
Increased AST	7 (16%)	2 (5%)
Stomatitis	8 (18%)	2 (4%)
Diarrhea	4 (9%)	-
Pneumonitis	4 (9%)	-

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

CDK4/6 inhibitor exposure, which included 192 patients, reported a shorter median PFS for patients with prior CDK4/6 inhibitor use [median PFS of 3.4 months (prior CDK4/6 inhibitor use) vs 5.4 months (no prior CDK4/6 inhibitor use), p=0.013].[12] In another retrospective cohort study with a similar design, the median PFS was 3.6 months in patients with prior CDK4/6 inhibitor exposure and 4.5 months in those without CDK4/6 inhibitor exposure; however, the difference in PFS was nonsignificant, likely because of the small sample size (43 patients).[13] Similarly, another retrospective analysis reported a shorter median PFS for everolimus plus exemestane therapy in patients with previous CDK4/6 inhibitor exposure than in those with no previous CDK4/6 inhibitor exposure.[14]

In the present study, liver and pleural/peritoneal metastases were associated with shorter PFS (median=2.9 months) in patients who received everolimus plus endocrine therapy. Subgroup analysis in the BOLERO-2 trial revealed that patients benefitted from the addition of everolimus, regardless of the visceral metastasis status.[10] Therefore, the shorter PFS in patients with liver and pleural/peritoneal metastases observed in our study can be attributed to the poor prognosis associated with these particular subgroups. Nevertheless, considering the notably brief PFS period observed in such patients, it may be prudent to prioritize alternative treatment options for individuals with liver or pleural/peritoneal metastases.

The present study observed more hematological adverse events than previously reported. Anemia (45% in our study vs. 21% in BOLERO-2), leukopenia (50% vs. 6%), and neutropenia (34% vs. 8%) had higher prevalence in our study cohort than in BOLERO-2.[15] This may be partly due to the high prevalence of other hematological conditions, such

as iron deficiency anemia and ethnic neutropenia, in the Bahraini population.[16,17] Moreover, pharmacokinetic and/or pharmacogenetic differences may affect sensitivity to hematological side effects of everolimus.

Nonetheless, this study had some limitations. First, the relatively small sample size may have reduced the statistical power to detect differences in PFS among subgroups. Second, the heterogeneity of the patient population, which reflects the real-world setting, increases variations in clinical parameters, such as menopausal status and concurrent endocrine treatments alongside everolimus therapy. Finally, our study was conducted in a specific population that may not be representative of other populations.

CONCLUSION

In conclusion, this study showed that everolimus plus endocrine therapy has a moderate effect on PFS in patients with MBC who received prior combination treatment with a CDK4/6 inhibitor and a hormonal agent. The effect is more pronounced in patients without liver or pleural/peritoneal metastases.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Zeki Gökhan Sürmeli;* ***Design:*** *Zeki Gökhan Sürmeli, Muhammad Sajid, Samrin Liaqat, Nawaf Mohammed Alkhalfan;* ***Control/Supervision:*** *Zeki Gökhan Sürmeli;* ***Data Collection and/or Processing:*** *Muhammad Sajid, Samrin Liaqat, Nawaf Mohammed Alkhalfan;* ***Analysis and/or Interpretation:*** *Zeki Gökhan Sürmeli, Muhammad Sajid, Samrin Liaqat, Nawaf Mohammed Alkhalfan;* ***Literature Review:*** *Zeki Gökhan Sürmeli;* ***Writing the Article:*** *Zeki Gökhan Sürmeli, Muhammad Sajid, Samrin Liaqat, Nawaf Mohammed Alkhalfan;* ***Critical Review:*** *Zeki Gökhan Sürmeli, Muhammad Sajid, Samrin Liaqat, Nawaf Mohammed Alkhalfan.*

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