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Research article

THERAPEUTIC RESPONSE AND TOXICITY OF CYCLIN-DEPENDENT KINASE 4/6 INHIBITORS IN THE TREATMENT OF HORMONE RECEPTOR-POSITIVE, HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2 NEGATIVE METASTATIC BREAST CANCER– A SINGLE-CENTER EXPERIENCE

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SUMMARY

Background: *The aim of the study was to determine the therapeutic response and toxicity of CDK 4/6 inhibitor therapy in patients with hormone-positive HER2-negative metastatic breast cancer. Additional aims were to determine whether there is a difference in survival and response to therapy in relation to age, ECOG status, other visceral diseases, the length of time waiting for drug approval, side effects, and consequently, treatment interruption and dose reduction.*

Methods: *The study analyzed all available medical documentation for 65 patients who were treated with CDK 4/6 inhibitors for hormone receptor-positive HER2-negative metastatic breast cancer at the Oncology Clinic of the University Clinical Hospital Mostar during the period from January 1, 2020, to December 31, 2023. Data for analysis were obtained by processing the medical documentation. Additionally, data were obtained from the Federal Fund of the Health Insurance and Reinsurance Institute of the Federation of Bosnia and Herzegovina. A retrospective cohort study was conducted based on the obtained data.*

Principal conclusion: *There was no statistically significant difference in response to therapy regarding PFS between patients who received CDK 4/6 inhibitors in four different therapeutic lines. However, a statistically significant difference in OS was found, i.e., patients who received this therapy in the first and second lines of treatment had longer survival compared to those who received therapy in later lines, partially confirming the hypothesized hypothesis.A statistically significant majority of patients on CDK 4/6 inhibitor therapy did not experience side effects, thus confirming the hypothesis.*

Key words: *Breast Neoplasms, Neoplasm Metastasis, Cyclin-Dependent Kinase Inhibitor*

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INTRODUCTION

Breast cancer is the leading type of cancer among women worldwide, accounting for about one-quarter of all cancer cases in women (1). Its incidence is rising worldwide, with the highest rates observed in developed countries, where nearly half of all cases are found. This increase is largely attributed to factors associated with a western lifestyle, such as unhealthy diet, smoking, excessive stress, and lack of physical activity. Despite advances in diagnosis and treatment, breast cancer remains the leading cause of cancer-related mortality among women worldwide, with the highest mortality rates in developing countries, which is attributed to inadequate screening and treatment options. Breast cancer risk is influenced by gender, age, economic development, hormonal factors (estrogen exposure, reproductive history, breastfeeding), genetics, hormone replacement therapy, diet, obesity, and factors like hormonal birth control, alcohol, and ionizing radiation(2). Breast cancer develops from DNA damage and genetic mutations, often worsened by estrogen exposure. In some cases, inherited gene mutations like BRCA1 and BRCA2 increase the risk. Normally, the immune system eliminates abnormal cells, but in breast cancer, this defense is compromised, leading to uncontrolled tumor growth and metastasis (3).

Hormone receptor-positive and HER2-negative (HR+/HER2-) breast cancer is common, representing two-thirds of advanced or metastatic cases. When diagnosed early, it has a better prognosis. For metastatic HR+/HER2- breast cancer, endocrine therapy (ET) is often combined with CDK inhibitors like palbociclib, ribociclib, and abemaciclib, which have shown clinical benefits (4).Cyclin-dependent kinases (CDKs) play a crucial role in regulating the progression of the cell cycle and the final cell division. Palbociclib, ribociclib, and

abemaciclib are orally administered, highly selective, and reversible CDK4 and CDK6 inhibitors. They are used in the treatment of metastatic breast cancer with hormone receptor-positive (HR+), HER2-negative receptors, along with specific hormonal therapy (5). CDK4/6 inhibitors block the G1-S transition in the cell cycle, which is regulated by cyclins D, CDK4, and CDK6. These cyclins activate CDK4/6, leading to the phosphorylation of pRb, releasing its inhibition on E2F transcription factors and allowing cell division. In hormone receptor-positive breast cancer, cyclin D overexpression and intact pRb function make this checkpoint a key target for therapy. CDK4/6 inhibitors stop the cell cycle at this stage (6). These therapies extend progression-free survival (PFS), delay chemotherapy, and improve quality of life. However, they do not provide a cure, as cancer eventually progresses, and some cancers show resistance (4).Phase II and III clinical trials have shown that combining CDK4/6 inhibitors with hormonal therapy (HT) significantly extends progression-free survival (PFS) compared to hormonal therapy alone, with an acceptable toxicity profile. However, overall survival (OS) benefits have not been proven as a primary endpoint. In the PALOMA study, OS was numerically longer with palbociclib, but not statistically significant(7). All three CDK4/6 inhibitors have been tested with various AIs in first-line therapy and with fulvestrant in second-line therapy for HER2-negative metastatic breast cancer. Palbociclib with letrozole nearly doubled median PFS in the PALOMA-1 study, leading to FDA approval. Ribociclib with letrozole also extended PFS in the MONALEESA-2 study, and abemaciclib showed similar results in the MONARCH-3 study.

For patients resistant to endocrine therapy (ET), CDK4/6 inhibitors combined with fulvestrant significantly extended PFS. In the PALOMA-3 study, palbociclib with fulvestrant extended PFS, and abemaciclib showed similar benefits in the MONARCH-2 study.

CDK4/6 inhibitors like ribociclib have also been studied in premenopausal women, with the MONALEESA-7 study showing significant PFS extension. Additionally, abemaciclib's use in a neoadjuvant setting in the neoMONARCH study showed a significant reduction in Ki-67 expression (8).

New molecular changes induced by CDKi therapy may reduce the effectiveness of future treatments. Additionally, overactivation of the PI3K pathway, common in HR+/HER2- metastatic breast cancer, can lead to resistance to ET and CDKi. While PI3K inhibitors have been effective for tumors with PI3K mutations after CDKi therapy, it's unclear if targeting this pathway can prevent resistance. Rapid disease progression after stopping CDKi highlights the need for better understanding and more refined treatment strategies, as there are no clear clinical guidelines for post-CDKi therapies (4). The aim of the study was to determine the therapeutic response and toxicity of CDK 4/6 inhibitor therapy in patients with hormone-positive HER2-negative metastatic breast cancer.

Other objectives included assessing whether survival and therapy response vary based on age, ECOG status, other visceral conditions, the duration of waiting for drug approval, side effects, and treatment interruptions or dose reductions. Additionally, the study aimed to examine the occurrence of side effects during treatment (such as neutropenia, elevated liver transaminases, thrombocytopenia, etc.) and determine if there are differences in side effects between different CDK 4/6 inhibitors.

SUBJECTS AND METHODS

The study analyzed all available medical documentation for 65 patients who were treated with CDK 4/6 inhibitors for hormone receptor-positive HER2-negative metastatic breast cancer at the Oncology Clinic of the University Clinical Hospital Mostar during the period from January 1, 2020, to December 31, 2023.

Data Collection and Processing Methods

Data for analysis were obtained by processing the medical documentation from the Oncology Clinic of the University Clinical Hospital Mostar, primarily by reviewing medical histories and the hospital's information system. Additionally, data were obtained from the Federal Fund of the Health Insurance and Reinsurance Institute of the Federation of Bosnia and Herzegovina.

A retrospective cohort study was conducted based on the obtained data.

The following characteristics were analyzed:

Hormone receptor status (ER, PgR), HER-2 receptor expression, proliferation index Ki-67, age at diagnosis of metastatic disease, age at initiation of CDK 4/6 inhibitor therapy, year of therapy initiation, menopausal status, comorbidities, therapeutic line for metastatic disease, partner therapy with CDK 4/6 inhibitor (fulvestrant or any aromatase inhibitors), use of LHRH agonists in premenopausal women, number of metastatic sites, location of metastases (bones, liver, etc.), previous therapies, time from metastatic disease diagnosis to initiation of the indicated therapy, ECOG status before treatment initiation, PFS (Progression-Free Survival), patient status (progression),response to therapy (stable disease, partial regression, complete regression, progression), side effects during treatment, hematological toxicity, elevated liver transaminases, treatment discontinuation due to toxicity, dose reduction due to toxicity, OS (Overall Survival),patient status (death).

Statistical Data Analysis

The results of the statistical analysis of categorical data are presented in tables as absolute and relative frequencies, while numerical data are displayed as mean ± standard deviation (for parametric data) or as median and interquartile range (for non-parametric data). The significance of differences in categorical data was tested using the χ^2 test or Fisher's exact test, and for numerical data using the Student's t-test for independent samples and one-way ANOVA test (for parametric data) or the Mann-Whitney test and Kruskal-Wallis test (for non-parametric data). Statistical analysis of the collected data was conducted using IBM SPSS Statistics software (version 25.0, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA). Differences between groups were considered statistically significant for $p < 0.05$.

RESULTS

No statistically significant difference in therapy response was found between patients who received CDK 4/6 inhibitors in four different therapeutic lines (Table 1).

Table 1. Comparison of therapy response between patients who received CDK 4/6 inhibitors in different therapeutic lines.

Best Response	**First Line**	**Second Line**	**Third Line**	**Fourth Line**	**χ^2**	**p***
Progression of disease	3 (7.0%)	1 (7.7%)	1 (14.3%)	1 (50.0%)	7.629	0.608
Stable disease	15 (34.9%)	4 (30.8%)	3 (42.9%)	0 (0.0%)		
Partial regression	24 (55.8%)	7 (53.8%)	3 (42.9%)	1 (50.0%)		
Complete response	1 (2.3%)	1 (7.7%)	0 (0.0%)	0 (0.0%)		

Fisher's exact test

Patients who received CDK 4/6 inhibitors in the first and second lines had statistically significantly longer overall survival compared to patients who received the treatment in the third and fourth lines (Table 2).

Table 2. Comparison of overall survival between patients who received CDK 4/6 inhibitors in different therapeutic lines.

	Therapeutic line									
Overall survival	first		second		third		fourth		χ^2	p*
	n	%	n	%	n	%	n	%		
yes	36	83,7	11	84,6	3	28,6	0	0,0	13,580	**0,001**
no	7	16,3	2	15,4	5	71,4	2	100,0		

**Fisher's exact test*

No statistically significant difference in treatment response was observed between patients receiving palbociclib and those receiving ribociclib (Table 3).

Table 3. Comparison of treatment responses between patients receiving two different CDK 4/6 inhibitors.

	CDK 4/6 inhibitor					
	palbociklib		ribociklib		χ^2	p*
Best response	n	%	n	%		
Disease progression	3	9,1	3	9,4		
Stable disease	12	36,4	10	31,4	1,927	0,671
Partial regression	18	54,5	17	53,1		
Complete response	0	0,0	2	6,3		

**Fisher's exact test*

There was no statistically significant difference in overall survival between patients
treated with palbociclib and those treated with ribociclib (Table 4).

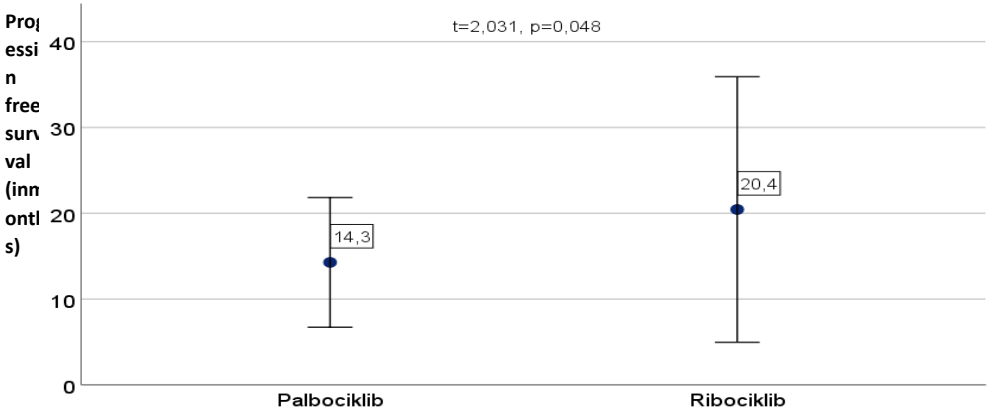
Table 4. Comparison of overall survival between patients treated with two different CDK 4/6 inhibitors.

	CDK 4/6 inhibitor					
Overall survival	palbociklib		ribociklib		χ^2	p*
	n	%	n	%		
yes	25	75,8	24	75,0	0,005	1,000
no	8	24,2	8	25,0		

** Fisher's exact test*

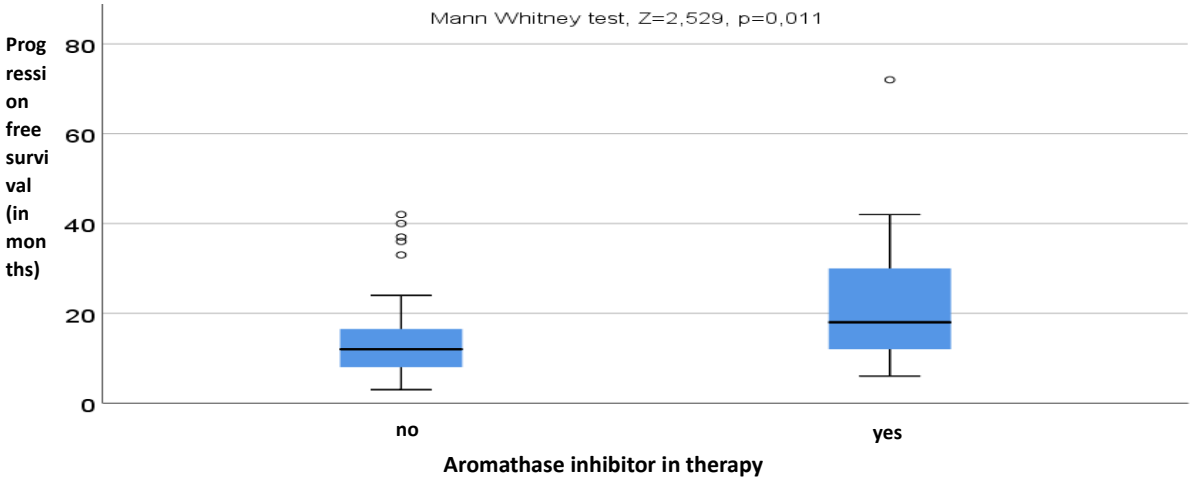
Patients receiving ribociclib had a statistically significantly higher PFS compared to patients receiving palbociclib (Figure 1). There was no statistically significant difference in OS (t-test, t=0.656, p=0.514) between patients receiving palbociclib (24.6 ± 20.8) and those receiving ribociclib (28.5 ± 26.4).

Figure 1. Comparison of progression-free survival between patients receiving two different CDK 4/6 inhibitors.



Patients who received a CDK 4/6 inhibitor along with a second aromatase inhibitor had a statistically significantly higher PFS compared to patients who did not receive a second aromatase inhibitor (Figure 2).

Figure 2. Comparison of progression-free survival between patients receiving a CDK 4/6 inhibitor along with a second aromatase inhibitor.



The statistically significant majority of patients on CDK 4/6 inhibitor therapy did not experience side effects (Figure 3).

Figure 3. Comparison of the number of patients with and without side effects caused by CDK 4/6 inhibitor therapy.

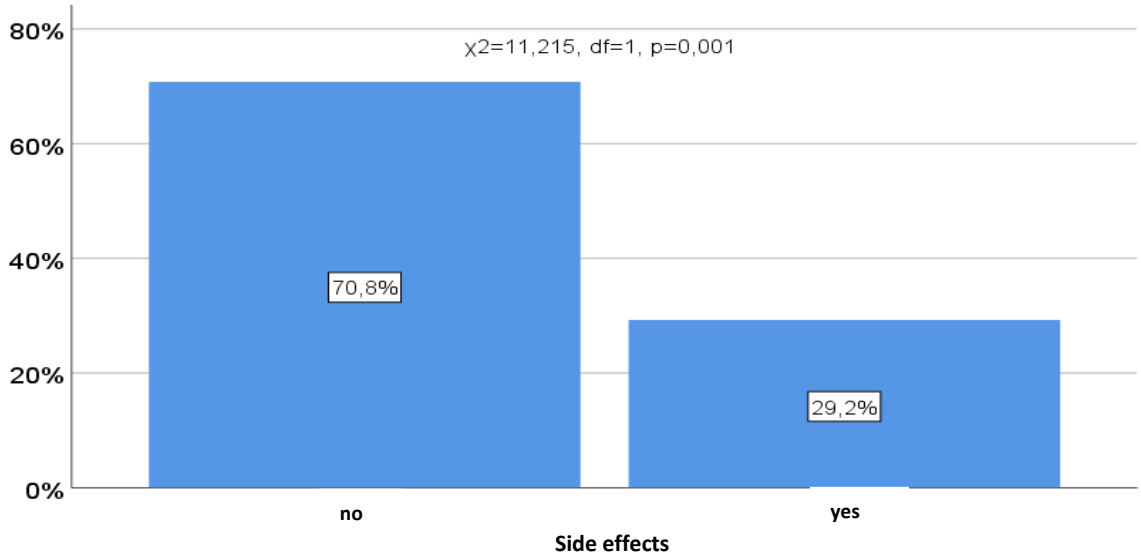


Table 5 shows the frequency of side effects experienced by patients in the study. Hematological toxicity was the most commonly recorded. We could not statistically calculate the differences between individual side effects, as the distribution of side effects among the patients was uneven, i.e., in the patients of this study, not only one type of side effectwas recorded, but multiple or none at all.

Table 5. Overview of side effects experienced by patients in the study.

Side effects	n	%
Hematological toxicity	18	27,6
Elevated liver transaminases	1	1,53
Discontinuation of therapy due to toxicity	14	21,5
Dose reduction due to toxicity	18	27,7
Neutropenia	16	24,6
Trombocytopenia	4	6,2
Other	2	3,1

We also compared the number of specific side effects during the use of different CDK 4/6 inhibitors. Since there was no statistically significant difference in the occurrence of any individual side effect between the two drugs, those results were not presented.

There was no statistically significant difference in the age at which metastatic disease was confirmed and the age at which treatment was started between surviving and deceased patients (Table 6).

Table 6. Comparison of the age at which metastatic disease was confirmed and the age at which treatment was started between surviving and deceased patients.

	Death				t	p
	yes (n=16)		no (n=49)			
	x̄	SD	x̄	SD		
The age at which metastatic disease was confirmed	57,75	10,847	61,92	10,352	1,382	0,172
The age at which treatment with CDK 4/6 inhibitors began	60,2	10,847	62,37	10,319	0,704	0,484

DISCUSSION

Statistical analysis of the data from this study revealed that there was no statistically significant difference in the response to therapy (PFS) between patients who received CDK 4/6 inhibitors in four different therapeutic lines. However, a statistically significant difference in OS was found between patients who received CDK 4/6 inhibitors in different therapeutic lines, partially confirming the hypothesis of this study. Patients treated with CDK 4/6 inhibitors in the first and second lines of treatment had statistically significantly longer survival compared to those who started treatment with this therapy in later lines. Additionally, as we anticipated, the majority of patients did not experience side effects during treatment with CDK 4/6 inhibitors.

Studies that have established CDK 4/6 inhibitors as the first therapeutic option in patients with metastatic hormone receptor-positive, HER2-negative breast cancer have shown a benefit for this therapy regarding PFS and OS (9, 10-12). As noted, our study confirmed this for OS, but not for PFS. This may be explained by the small sample size, short follow-up period, and variability in treatment response among the patients.

It is important to emphasize once again that the hypothesis was confirmed that the majority of patients would not experience side effects during treatment with CDK 4/6 inhibitors. Also, among the most frequently reported side effects, neutropenia was the most common, which aligns with results from previous studies (9, 11-12).

Regarding other results, it should be noted that PFS was statistically significantly higher in patients who received ribociclib compared to those who received palbociclib, although no such difference was observed for OS.

As for other studies on this topic, a similar study conducted in Italy investigated PFS and OS in patients treated with endocrine therapy and various CDK 4/6 inhibitors. It was found that ribociclib showed a statistically significant improvement in OS, but palbociclib did not. We can observe that the results of our study differ from those of the study conducted in Italy. The heterogeneity test suggests that the different OS results among the different CDK 4/6 inhibitors could be explained by chance (10).

The limitations of this study include a small number of participants, a short follow-up period, and the single-center nature of the study, all of which should be considered when analyzing and interpreting the data obtained.

To obtain more detailed results, future studies will require prospective research with a larger number of participants, as well as the inclusion of patients from multiple centers (i.e., multicenter studies) to reduce bias and increase the general applicability of the results.

It would also be very important to investigate how CDK 4/6 inhibitor therapy affects tumor biology to identify biomarkers of resistance and optimize therapy. Special attention should be paid to the molecular characterization of tumors before and after the use of CDK inhibitors. Understanding the molecular mechanisms of intrinsic and acquired resistance could present a new approach in the application of CDK 4/6 inhibitors.

In conclusion, we can say that this study confirmed the hypothesis that OS is significantly higher in patients who started therapy with CDK 4/6 inhibitors in the first and second lines of treatment, compared to those who started the therapy in later lines. This was not confirmed for PFS. Additionally, the majority of patients did not experience side effects during treatment, confirming that this is a well-tolerated therapeutic option.

All these results show and confirm that CDK 4/6 inhibitor therapy is a safe and optimal treatment strategy for patients with metastatic hormone receptor-positive, HER2-negative breast cancer, and that earlier inclusion of this therapy certainly contributes to improving the quality

of life, delaying the use of more toxic therapeutic options such as chemotherapy, and having an overall positive impact.

CONCLUSION

In this study, there was no statistically significant difference in response to therapy regarding PFS between patients who received CDK 4/6 inhibitors in four different therapeutic lines. However, a statistically significant difference in OS was found, i.e., patients who received this therapy in the first and second lines of treatment had longer survival compared to those who received therapy in later lines, partially confirming the hypothesized hypothesis.A statistically significant majority of patients on CDK 4/6 inhibitor therapy did not experience side effects, thus confirming the hypothesis.

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