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CDK4-6 Inhibitors: Evaluation of Efficacy in Cases of Hormone Receptor-Positive HER2-Negative Breast Cancer with Only Bone Metastasis

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ABSTRACT

Objective: Bone is the most common site of metastasis in patients with hormone receptor (HR)-positive breast cancer. However, 17-37% of these patients with metastatic disease develop metastasis only in the bone. In this context, the present study aimed to compare the CDK4-6 inhibitors palbociclib and ribociclib in terms of their efficacy in treating HR-positive human epidermal growth factor receptor 2 (HER-2)-negative breast cancer patients with only bone metastases detected at diagnosis.

Material and Methods: The study was conducted as a retrospective observational study of 31 patients with HR-positive and HER2-negative breast cancer and only bone metastases who were treated with CDK4-6 inhibitors. The patients were divided into two groups based on the CDK4-6 inhibitor used and subjected to overall survival (OS) analysis.

Results: The median age of the patients included in the present study was 57 years (36-76). The median OS in the ribociclib group was 25.46 months [confidence interval (CI) was not reached in the Kaplan-Meier analysis]. The median OS in the palbociclib group was 16.07 months (95% CI: 7.88-24.25). The difference in OS between the two groups was statistically significant (p=0.043). Among the other variables with the potential of affecting the OS of these patients, the N stage and survival values were observed to be significantly different (p=0.033) between the two groups. The multivariate analysis revealed the N stage (p=0.011) and the type of CDK4-6 inhibitor used (p=0.023) as the independent risk factors that affected the OS of these patients.

Conclusion: In patients with hormone-positive HER2-negative breast cancer with only bone metastasis, ribociclib administration achieved increased OS compared to the use of palbociclib.

Keywords: Breast cancer; hormone-positive cancer; bone metastasis; CDK4-6 inhibitors

INTRODUCTION

Breast cancer is the most frequently detected cancer in women worldwide and also the most common cause of death caused by cancer in women.[1] Approximately 80% of the patients with breast cancer are hormone receptor (HR)-positive at the time of diagnosis.[2] The introduction of endocrine therapies has particularly increased survival in metastatic HR-sensitive breast cancer. Endocrine therapies are less toxic compared to chemotherapy while leading to similar survival rates, due to which these therapies are used as the first-line treatment of these patients.[3]

The most effective and recommended first-line endocrine therapy is the use of a combination of a cyclin-dependent kinase (CDK) 4-6 inhibitor, such as palbociclib, ribociblib, and abemaciclib, and an aromatase inhibitor (AI) or tamoxifen (TMX) along with luteinizing hormone-releasing hormone (LHRH) analogs.[4-7] Few studies have, however, demonstrated

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that the efficacy of one of these CDK4-6 inhibitors is superior to the others. However, the drug side effect profiles of these agents are slightly different, and patient comorbidities should be considered when using these drugs for treatment.

Bone is the most common organ to which HR-positive breast cancer cells have been observed to be metastasized.[8] According to the autopsy results of patients diagnosed with breast cancer, approximately 70% of these patients develop bone metastasis.[9] In contrast, cases of only bone metastasis are scarce, accounting for just 17%-37% of patients with metastatic disease.[10] Moreover, this group of patients is reported to have a much better prognosis than the patients with bone metastases along with other systemic metastases.[11]

The present study aimed to compare the CDK4-6 inhibitors palbociclib and ribociclib in terms of their effectiveness in treating patients with HR-positive breast cancer with only bone metastasis detected at the time of diagnosis.

MATERIAL AND METHODS

The present study was designed as a retrospective observational study that enrolled 31 patients who were admitted to our clinic between May 2019 and June 2023, were older than 18 years, had only bone metastasis at the time of diagnosis, were HR-positive in biopsy results, were HER2-negative, and administered CDK4-6 inhibitors as treatment. The patients with no metastasis detected at the time of diagnosis, a non-bone metastasis, age less than 18 years, HER2-positivity, and not treated with CDK4-6 inhibitors were excluded from the study. Since the earliest response imaging examinations of the patients were conducted in the third month after the commencement of treatment, each patient received CDK4-6 inhibitors for at least three months. Since all patients in the study had bone metastasis, all of them received either zolendronic acid or denosumab. All retrospective data on clinical characteristics, pathology and laboratory results, and treatment data were retrieved from the medical records of patients. The limit values used in our laboratory were used as threshold values for the laboratory parameters. A receiver operating curve (ROC) analysis was conducted to determine the threshold values of estrogen receptor (ER), progesterone receptor (PR), and Ki-67. The time between the commencement of treatment and death due to any cause was utilized to determine the overall survival (OS) of the patients.

Since the study was designed as a retrospective one, the study was approved by the Ankara Bilkent City Hospital Ethics Committee for Clinical Research at our Hospital (date: February 28, 2024, no: 24-33) without the requirement of obtaining informed consent from the patients. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 25 (USA). Normal distributions were determined using histograms and the Shapiro-Wilk test. Continuous variables with normal distribution were expressed as means ± standard deviations, while the variables with a non-normal distribution were expressed as median (minimum-maximum) values. The continuous variables were compared between the two groups using the Mann-Whitney U test. A chi-squared or Fisher's exact test was conducted to compare categorical variables. The threshold values were determined based on the ROC analysis. Kaplan-Meier and Cox regression analyses were performed for survival and prognostic factors. $P<0.05$ was considered the threshold of statistical significance.

RESULTS

The median age of patients in the present study was 57 years (age range 36 to 76 years). The median follow-up period was 13.67 months (4.11 to 39.13 months). A total of 11 (35.5%) patients among all the patients who participated in the study died during the follow-up period. The median duration of the usage of CDK4-6 inhibitors was 12.9 (4.1 to 39.13) months.

The ROC analysis revealed the following threshold values for ER, PR, and Ki-67: 91% for the ER percentage [area under curve (AUC): 0.564, sensitivity: 50.0%, specificity: 54.5%, p=0.563], 67.5% for the PR percentage (AUC: 0.634, sensitivity: 60.0%, specificity: 63.6%, p: 0.223), and 22.5% for Ki-67 (AUC: 0.655, sensitivity: 65.0%, specificity: 63.6%, p=0.16). The insignificant p-values in the ROC analysis could be explained by the small sample size of the study.

Further, 28 patients (90.3%) among all patients included in the study received CDK4-6 inhibitors as the first-line treatment, while 3 patients (9.7%) received this treatment as the second-line treatment. A total of 14 (45.2%) patients received ribociclib, while 17 patients (54.8%) received palbociclib. None of the patients had undergone surgery for their primary breast tumor. Three patients (9.7%) were subjected to palliative radiotherapy for the bones. The baseline characteristics of patients are presented in Table 1.

The patients who received ribociclib or palbociclib were divided into two groups and compared in terms of their age, clinical T stage, clinical N stage, ER percentage, PR percentage, pathologic grade, Ki-67 percentage, CEA, and CA15.3. The comparative analysis revealed no statistically significant differences between the two groups in any of the variables (Table 2). Further, for supportive bone therapy, 23

TABLE 1: Baseline characteristics of all patients.	
Age, years	57 (36-76)
Eastern Cooperative Oncology Group, performance status	
0	14 (45.2%)
1	15 (48.4%)
2	2 (6.5%)
T stage	
1-2	18 (58.1%)
3-4	13 (41.9%)
N stage	
0-1	8 (25.8%)
1-2	23 (74.2%)
Estrogen receptor percent	
≥90	22 (71.0%)
<90	9 (29.0%)
Progesterone receptor percent	
≥67	16 (51.6%)
<67	15 (48.4%)
Kİ-67	
≥22.5	17 (54.8%)
<22.5	14 (45.2%)
Carcinoembryonic antigen	
≥2.5	17 (56.7%)
<2.5	13 (43.3%)
CA15.3	
≥32.4	16 (53.3%)
<32.4	14 (46.7%)
Radiotherapy to bone	
Yes	3 (9.7%)
No	28 (90.3%)
Time to treatment with CDK4-6 inh	
First line	28 (90.3%)
Second line	3 (9.7%)
CDK4-6 inhibitor	
Ribociclib	14 (45.2%)
Palbociclib	17 (54.8%)
CA: Cancer antigen; CDK: Cyclin-dependent kinase.	

(74.2%) patients received zolendronic acid, and 8 (25.8%) patients received denosumab. Denosumab treatment was administered to 4 patients in the ribociclib group (28.6%) and 4 patients in the palbosiclib (23.5%) group.

The median OS in the ribociclib group was 25.46 months (confidence interval was not reached in the Kaplan-Meier analysis). The median OS in the palbociclib group was 16.07 months (95% CI: 7.88 to 24.25). There was a statistically significant difference between the two groups (p=0.043) (Figure 1).

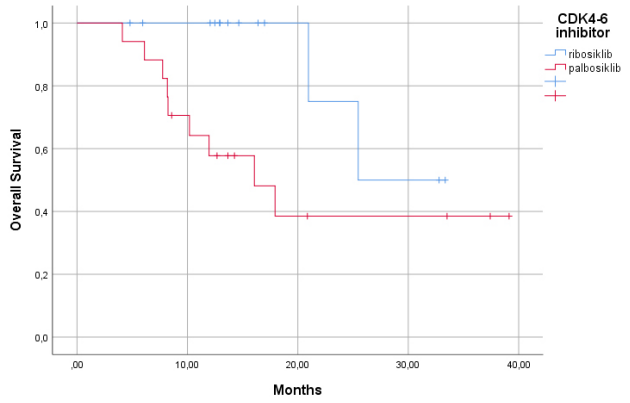

FIGURE 1: Kaplan-Meier survival curves for overall survival of CDK4-6 inhibitor groups.

CDK: Cyclin-dependent kinase

The other variables that could affect OS, such as age (p=0.791), clinical T stage (p=0.059), ER percentage (p=0.323), PR percentage (p=0.301), tumor grade (p=0.945), Ki-67 in pathology (p=0.194), CEA level (p=0.417), CA15.3 level (p=0.251), and the line of treatment in which the CDK4-6 inhibitor was used (p=0.932), were not significantly different between the groups. Only the clinical N stage variable presented a statistically significant difference with OS (p=0.033). The multivariate analysis revealed the N stage (p=0.011) and the type of CDK4-6 inhibitor used (p=0.023) as the independent risk factors affecting OS (Table 3).

DISCUSSION

The present study aimed to evaluate the effectiveness of CDK4-6 inhibitors in patients with HR-positive and HER2-negative breast cancer with only bone metastasis. According to the results of the study, the use of ribociclib increased OS compared to the use of palbociclib in these patients.

Recent advances in endocrine therapies have led to the adoption of the combination of CDK4-6 inhibitors and TMX or AI along with LHRH analogs as the standard of care in the initial treatment of patients with metastatic HR-positive and HER2-negative breast cancer, except for patients with visceral crisis. This treatment modality leads to an efficacy similar to that achieved using chemotherapy while the side effects are considerably reduced.[12] In the present study, all patients were treated with the CDK 4-6 inhibitor ribociclib or palbociclib, and most of these patients received the drugs as first-line treatment.

Several previous studies have compared the efficacy of different CDK4-6 inhibitors in patients with metastatic HR-positive breast cancer. Zhao et al.[13] indirectly compared the patients participating in the PALOMA-2, MONALEESA-2,

TABLE 2: Association between the CDK4-6 inhibitors and features of patients.

Variables	CDK4-6 inhibitor		p value
	Ribociclib: n, (%)	Palbociclib: n, (%)	
Age			
≤58	7 (50)	9 (52.9)	0.999
>58	7 (50)	8 (47.1)	
T stage			
1-2	11 (78.6)	7 (41.2)	0.067
3-4	3 (21.4)	10 (58.8)	
N stage			
0-1	4 (28.6)	4 (23.5)	0.999
2-3	10 (71.4)	13 (76.5)	
Estrogen receptor percent			
≥90	10 (71.4)	9 (52.9)	0.461
<90	4 (28.6)	8 (47.1)	
Progesterone receptor percent			
>67	8 (57.1)	8 (47.1)	0.722
≤67	6 (42.9)	9 (52.9)	
Grade			
1-2	13 (92.9)	11 (64.7)	0.062
3	1 (7.2)	6 (35.3)	
Ki-67			
<22.5	5 (35.7)	9 (52.9)	0.473
≥22.5	9 (64.3)	8 (47.1)	
Carcinoembryonic antigen			
<2.5	7 (53.8)	6 (35.3)	0.460
≥2.5	6 (46.2)	11 (64.7)	
CA15.3			
<32.4	7 (53.8)	7 (41.2)	0.713
≥32.4	6 (46.2)	10 (58.8)	

CA: Cancer antigen; CDK: Cyclin-dependent kinase.

and MONARCH-3 trials and reported no difference in OS or PFS between patients receiving ribociclib, palbociclib, or Abemaciclib. Xie et al.[14] reported no difference in OS or PFS between the different CDK4-6 inhibitor subtypes in 4,580 patients. No study in the literature has, to the best of the author's knowledge, demonstrated to date that either of the above two drugs leads to better outcomes in terms of OS than the other. However, in the recently reported results of the survival analyses from PALOMA and MONALEESA trials, no statistically significant difference in OS was stated upon the use of palbociclib, while OS was significantly higher with the use of ribociclib.[15,16] In the present study, as well, a higher OS was observed in patients who received ribociclib.

A meta-analysis of patients with HR-positive and HER2-negative breast cancer with only bone metastasis revealed that the treatment of choice should be the same as the one used for patients with other metastatic hormone-positive cancers.[17] Survival in these patients is better than that in patients with bone metastasis who also have visceral metastases.[18] Studies have demonstrated that variables such as previous use of bisphosphonate, presence or absence of symptoms, number of bone metastases, and treatment modalities affect survival in this group of patients.[11,18] No study has, to the best of the author's knowledge, compared the efficacy of CDK4/6 inhibitors in these patients to date. The present study demonstrated that in this group of patients, the use of ribociclib leads to better OS than the use of palbociclib.

TABLE 3: Prognostic factors of overall survival in patients.	
Univariable analysis	
Variables	**p value**
Age, ≤50 vs. >50	0.791
Clinical T stage, 1-2 vs. 3-4	0.059
Clinical N stage, 0-1 vs. 2-3	**0.033**
Estrogen receptor percent, <90 vs. ≥90	0.323
Progesterone receptor percent, <67 vs. ≥67	0.301
Grade, 1-2 vs. 3	0.945
Ki-67, <22.5 vs. ≥22.5	0.194
Carcinoembryonic antigen, <2.5 vs. ≥2.5	0.417
CA15.3, <32.4 vs. ≥32.4	0.251
Line of CDK4-6 inh, first vs second	0.932
CDK4-6 inh, ribociclib vs palbociclib	**0.043**
Multivariable analysis	
Variables	**p value**
N stage, 0-1 vs 2-3	**0.011**
CDK4-6 inh, ribociclib vs palbociclib	**0.023**
CA: Cancer antigen; CDK: Cyclin-dependent kinase; Inh: Inhibitor.	

Study Limitations

Certain limitations of the present study include the single-center setting, the small sample size, and the retrospective design.

CONCLUSION

Survival in patients with hormone-positive and HER2-negative breast cancer with only bone metastasis is better than that in other breast cancer groups. However, the literature on which drugs to select for this group of patients is scarce. In the present study, the use of ribociclib for this patient group resulted in much better OS than the use of palbociclib. However, larger studies have to be conducted to assess the effectiveness of different treatments in patients with hormone-positive and HER2-negative breast cancer with only bone metastasis.

Ethics

Ethics Committee Approval: Since the study was designed as a retrospective one, the study was approved by the Ankara Bilkent City Hospital Ethics Committee for Clinical Research at our Hospital (date: February 28, 2024, no: 24-33).

Informed Consent: The participants provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.C., D.U., Concept: S.S., Design: S.S., G.U., Data Collection or Processing: S.S., D.B., Analysis or Interpretation: M.M., B.C., Literature Search: Ö.B., E.A., Writing: S.S., M.M., Critical Review: F.T.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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