High Creatinine Level Secondary to Use of CDK 4/6 Inhibitor Treatment (Palbociclib and Ribociclib) + Endocrine Therapy (ET)

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ABSTRACT

The aim of this study is to share real-life data on the increase in creatinine due to CDK 4/6 inhibitor treatment and patients diagnosed with HR+/HER2-MBC and treated with ribociclib or palbociclib combined with ET were included in the study. While creatinine increase was observed in 17.9% (n = 19) of the 106 patients in the study population, 8.5% (n = 9) had Grade 1, 8.5% (n = 8) had Grade 2, and % 0.9 (n = 1) had Grade 3 creatinine elevation. The increase in creatinine occurred in 25% (n = 12) of ribociclib users and 12.1% (n = 7) of palbociclib users. No patient required a dose reduction or discontinuation of treatment due to elevated creatinine. Of the patients with high creatinine levels, 36.8% (n = 7) were over 65 years of age. Those with multiple comorbidities, blood urea nitrogen (BUN) >13.5 mg/dl, creatinine >0.66 mg/dl, BUN/creatinine ratio >19.95, glomerular filtration rate (GFR) >96.05 ml/min, and uric acid >4.69mg/dl. It was observed that the increase in the creatinine level was statistically significant (p <0.001). In conclusion, this study revealed that the increase in the serum creatinine secondary to ribociclib and palbociclib treatments is associated with kidney function tests and the number of concomitant diseases.

Key Words: *CDK 4/6 inhibitor, Creatinine elevation, Palbociclib, Ribociclib.*

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Cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors abemaciclib, palbociclib, and ribociclib,[1] which induce apoptosis in tumour cells by inhibiting cell cycle progression by arresting cells in the transition phase from G1 to S phase in the cell cycle. Combined endocrine therapy (ET) as a first-line treatment option in the treatment of hormone receptor (HR) positive human epidermal growth factor receptor-2 (HER-2) negative *de novo* MBC. It is also recommended as a second-line treatment in combination with ET in patients with progression while receiving adjuvant therapy or within 12 months after the end of adjuvant therapy.[1]

Although CDK 4/6 inhibitors may have common side effects as a class effect, drug-specific side effects are also seen due to the different CDK 4 and CDK 6 selectivities. Compared to palbociclib and ribociclib, abemaciclib has a different chemical structure. Abemaciclib's affinity for CDK 4 is 14 times higher than for CDK6. Therefore, in terms of dose-limiting toxicity (DLT) in Phase 1 studies, neutropenia was most commonly seen with palbociclib, diarrhoea and fatigue with abemaciclib, neutropenia, mucositis, asymptomatic thrombocytopenia, increased creatinine, and QTcF prolongation with ribociclib.[2]

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In the literature, no increase in creatinine level has been reported in the safety and side effect profile of ribociclib (Monaleesa 2 and 7) and palbociclib (Paloma 2 and 3) in Phase 3 studies.[2-4] Only the updated results of the Phase 3 Monaleesa-3 trial's study reported a 13% rate of all grade renal toxicity.[3] Also, in the phase 2 Monarch-2 study of abemaciclib, which consisted of 132 patients, the Grade 1 and 2 serum creatinine increase was 97.7%, while the Grade 3 serum creatinine increase was 0.8%.[5]

The study aimed to share the increase in creatinine level associated with ribociclib and palbociclib which has not been previously reported in the literature.

In this retrospective, cross-sectional study, patients diagnosed with HR+/HER2-MBC who were treated with ribociclib or palbociclib combined with ET at Dokuz Eylul University Hospital's Department of Medical Oncology between January 2020 and December 2021 were included. Patients who used nephrotoxic drugs or herbal products were excluded from the study.

Baseline serum creatinine was defined as the closest serum Cr level before the initiation of the CDK4/6 inhibitor. The authors used the common terminology criteria for adverse events (CTCAE) version 5.0 rating for acute kidney injury.

Descriptive statistics (mean ± standard deviation, percent %) were used in accordance with statistical analysis. In addition, Chi-square and Fisher's exact tests were used for categorical variables. The Kaplan-Meier method and Log-rank test were used for survival analysis. All data analyses were performed

using the social science statistical package (SPSS) version 24.0 and the variables were analysed at 95% confidence level and $p < 0.05$ was considered significant.

This study included 106 patients who received CDK 4/6 inhibitor combined with ET. The median age of the patients was 52.45 (26.26 - 90.25) years. One hundred and three (97.16%) of the population was female and 2.84% (n = 3) was male; 75.5% of the patients were postmenopausal.

Fifty-four point seven percent (n = 58) of the patients were treated with palbociclib, 45.3% (n = 48) were treated with ribociclib, and 44.3% (n = 47) of the whole group received combined treatment with AI (letrozole in 43.4% (n = 46) and anastrazole in 0.9% (n = 1); 55.7% (n = 59) were using combined treatment with fulvestrant.

The most common adverse event was neutropenia in 90.6% (n = 96) of the patients, followed by QTc prolongation in 46.2% (n = 49) and anaemia in 46.2% (n = 49), and an increase in creatinine level in 17.9% (n = 19) of the patients.

The increase in creatinine level was Grade 1 in 8.5% (n = 9) and Grade 2 in 8.5% (n = 9) of the study groups. Only one patient who was treated with CDK 4/6 inhibitor had Grade 3 creatinine elevation. The increase in creatinine occurred on the median 52 days (range: 18-307) and occurred in 25% (n = 12) of patients treated with ribociclib and 12.1% (n = 7) of patients treated with palbociclib. Of those patients with increased creatinine levels, 36.8% (n = 7) were 65 years of age and older.

Factors that may be associated with an increase in serum creatinine are shown in Table I.

Table I: The factors associated with the increased creatinine level.

Factors	Increase in creatinine / Normal creatinine total n = 19 / 87 n (%)	p-value
Age		
<65 years	12 / 68 (63.2%)	
≥65 years	7 / 19 (36.8%)	0.140
ECOG PS		
0	11 (74.7%)	0.218
1	5 (19.5%)	
2	3. (5.7%)	
Number of comorbidity		
Absent	2 (10.5 %)	<0.001
1 and above	15 (89.5%)	
BUN		
<13.5	3 / 49 (15.8 %)	0.001
≥13.5	16 / 38 (84.2%)	
Creatinine		
<0.66	2 / 46 (10.5%)	0.001
≥0.66	17 / 41 (89.5 %)	
BUN/Creatinin ratio		
<19.95	12 / 82 (63.2%)	0.001
≥19.95	7 / 5 (36.8%)	
GFR		<0.001
<96.05 ml/min	2 / 38 (10.5%)	
≥96.05 ml/min	17 / 49 (89.5 %)	
Uric acid		
<4.69	4 / 44 (23.5 %)	0.015
>4.69	13 / 35 (76.5%)	

The need for dose reduction developed in 21.7% (n = 23) of the patients. Due to the increase in creatinine, no dose reduction was made in the treatment of any patient and the treatment was not discontinued. In addition, there was no difference in response status between the patients who developed an increase in creatinine level and those who did not.

For HR+/HER2-MBC, class effect haematological and non-haematological side effects were observed at different rates due to first-line therapy CDK 4/6 inhibitors treatments,[3] and serum creatinine elevation is ribociclib (Monaleesa 2 and 7) and palbociclib (PALOMA 2 and 4) were not reported in the initial results of the Phase 3 studies.[2-4] However, in the updated results of the Phase 3 study Monaleesa-3 in which Ribociclib was combined with fulvestrant renal toxicity was reported as 13%.[3]

In Wilson *et al.*'s study of series of 32 patients, the increase in ribociclib-related creatinine level was reported to be 28%. In this study, the creatinine level seen in those receiving ribociclib was found to be close to the real-life data in the literature (36.8%, n = 7).[2]

For palbociclib, there is no study in the literature indicating an increase in creatinine. Only, a case report of decreased GFR in a 66-year old patient using fulvestrant with palbociclib was published.[4] In this study, palbociclib treatment was used predominantly (54.7%, n = 58), and an increase in creatinine was observed in. 12.1% of the patients.

When the relationship between high serum creatinine level and comorbidity was evaluated, one study showed that baseline comorbidity did not have a statistically significant effect,[3] whereas in this study, creatinine elevation was statistically significantly higher in patients with one or more comorbidities. There is no report on this subject in the literature, and Gupta *et al*. reported that two of the six patients who developed AKI had a GFR below 60 ml/min.[6]

In this study, 36.8% of the patients with elevated creatinine were aged 65 years and over, when the characteristics of the patients in the study of Gupta *et al*., in which six patients with acute kidney injury were reported and examined, which supports the result of this study; four of six patients were 65 years, or older.[6]

In this study, elevated serum creatinine and the factors affecting creatinine elevation due to palbociclib and ribociclib treatments, which were not directly addressed in Phase 3 studies, were revealed for the first time in the literature to the best of the authors' knowledge and there was no need for dose reduction or drug discontinuation due to high creatinine, it has been revealed that there is no relationship between the development of high creatinine and the response status.

ETHICAL APPROVAL:

The ethics committee approval was obtained from the Ethical Committee of the Dokuz Eylul University, Izmir, Turkiye, (Dated: 09.02.2022, Decision number: 2022/05-09).

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
MK: Data collection, writing original draft, editing, and writing reviews.
HSS: Statistical analysis.
TY: Supervision.
AK: Writing and critical review.
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