Evaluation of Factors That Increase the Risk of Hepatotoxicity in Patients Using Palbociclib and Ribociclib

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Abstract

Aim: In patients with hormone receptor-positive and HER2-negative metastatic breast cancer, the use of CDK 4/6 inhibitors in combination with endocrine therapy have become a standard of care.

Methods: This was a retrospective study involved patients over the age of 18 years, who had de novo metastatic or locally breast cancer progressed to the metastatic stage and were treated with ribociclib and/or palbociclib.

Results: The mean age of a total of 73 patients included in the study was 57.0±10.3 years. Thirty-four (46.6%) patients were treated with palbociclib, 35 (47.9%) patients with ribociclib, 4 (5.5%) with palbociclib and ribociclib. Twenty-five (34.2%) of the patients developed any grade of hepatotoxicity, 12 (16.4%) of them was grade 2 hepatotoxicity. Of these patients, 11 (44%) received palbociclib, 13 (52%) received ribociclib, and 1 (4%) received palbociclib and ribociclib. In patients who were treated with palbociclib, 1 (2.9%) developed grade 3 hepatotoxicity and 1 (2.9%) developed grade 4 hepatotoxicity. Of those who received ribociclib, 3 (8.5%) developed grade 3 hepatotoxicity and 2 (5.7%) developed grade 4 hepatotoxicity.

Conclusions: In conclusion, it can be stated that ribociclib is more toxic to the liver than palbociclib, since patients who received ribociclib and developed grade 3-4 hepatotoxicity had no disease that facilitates hepatotoxicity. We believe that more comprehensive studies are needed to determine the factors that facilitate hepatotoxicity such as liver metastasis and to select the drug accordingly will prevent patients from being devoid of this group of drugs and discontinuing their treatment due to toxicity.

Keywords: *Ribociclib, palbociclib, breast cancer, hepatotoxicity*

1. Introduction

Breast cancer is the most common cancer in women[1]. Nearly 75% of patients with breast cancer are hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative[2]. The 5-year survival rate for patients with stage 4 breast cancer is 20%[3]. While these patients are sensitive to endocrine therapies, they show progression after acquiring resistance[4,5]. Cyclin-dependent kinase (CDK) 4/6 inhibitors used with endocrine therapies have been shown to prolong progression-free survival (PFS) and overall survival (OS) in patients with metastatic breast cancer[6-9].

If there is no visceral crisis in patients with hormone receptor-positive and HER2- negative metastatic breast cancer, the use of CDK 4/6 inhibitors in combination with endocrine therapy have become a standard of care[10]. These drugs have brought about their specific side effects along with efficacy. The aim of this study is to evaluate hepatotoxicity with a moderate frequency in patients using palbociclib and ribociclib and factors that increase its risk.

2. Materials and methods

A total of 1152 patients who were admitted to Adana City Training and Research Hospital Medical On- cology Outpatient Clinic with a diagnosis of breast cancer between 01 January 2017 and 01 January 2022 were included in the retrospective analysis. Those with unavailable pathology information were excluded from the study. The treatments of patients with a pathological diagnosis of primary or metastatic breast cancer were evaluated. The study included a total of 73 patients over the age of 18 years who had de novo metastatic or locally advanced disease progressed to the metastatic stage and were treated with ribociclib and/or palbociclib. Informed consent was obtained from all individual participants or relatives

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included in the study. Patient data were analyzed through patient follow-up files and the hospital management system. The reported results of abdominal ultrasound examinations performed in the past 6 months before ribociclib or palbociclib treatment were evaluated. The hepatic steatosis grades of the patients were determined by taking into account the hepatic steatosis grades in abdominal ultrasound reports closest (0-3 months) to the time of drug initiation. Other toxicity grades were determined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

2.1. Statistical analysis

SPSS (Statistical Package for the Social Sciences) version 23.0 software package was used for statistical analysis of the data. Categorical measures were summarized using numbers and percentages, while continuous measures were summarized using the mean and standard deviation (median and minimum-maximum where appropriate). Chi-square and Fisher's exact tests were used to analyze categorical expressions. Shapiro-Wilk test was used to check whether the parameters included in the study follow a normal distribution. When parameters did not follow a normal distribution, Mann-Whitney U test was used for binary variables and Kruskal-Wallis tests were used for more than two groups. The level of statistical significance was set at 0.05 in all tests.

3. Results

The mean age of a total of 73 patients included in the study was 57.0±10.3 years. Of the patients, 68 (93.2%) were female and 5 (6.8%) were male. Thirty-four (46.6%) patients were treated with palbociclib, 35 (47.9%) patients with ribociclib, 4 (5.5%) with palbociclib and ribociclib. In patients who could not continue treatment due to toxicity even though there was no progression after the initiation of treatment, the treatment was switched, provided that consent for off-label use of another CDK inhibitor was obtained within the scope of the rules of the medicines regulatory authority. Therefore, 4 patients used both agents. In the same way, consent for off-label use was obtained for male patients. Of the patients, 22 (30.1%) had liver metastases, while 51 (69.9%) did not. Twenty-five (34.2%) of the patients developed any grade of hepatotoxicity, while 48 (65.8%) did not have any grade of hepatotoxicity. The median time from the end of cytotoxic chemotherapy to the initiation of CDK 4/6 inhibitor was 10 (0-120) months. The demographic characteristics and laboratory data of the patients are illustrated in Tables 1.

The mean age of the patients who developed hepatotoxicity was 56.3±8.3 years. Of these patients, 11 (44%) received palbociclib, 13 (52%) received ribociclib, and 1 (4%) received palbociclib and ribociclib. Out of these patients, 4 of patients using palbociclib; 5 of the patients using ribociclib were using concomitant fulvestrant treatment. Of those who were treated with palbociclib, 1 (2.9%) developed grade 3 hepatotoxicity and 1 (2.9%) developed grade 4 hepatotoxicity. Of those who received ribociclib, 3 (8.5%) developed grade 3 hepatotoxicity and 2 (5.7%) developed grade 4 hepatotoxicity. The demographic characteristics and laboratory data of the patients who developed hepatotoxicity are shown in Tables 2 and 3, respectively.

4. Discussion

In previous studies the 5-year survival rate for patients with metastatic breast cancer is around 20%[3]. While new targeted therapies have been introduced for the treatment of patients with HER2-positive metastatic breast cancer, the search for new treat-

Table 1

Demographic characteristics of patients

		Frequency (n)	Percentage (%)
Sex			
	Female	68	93.2
	Male	5	6,8
Ditribution of treatments			
	Palbociclib	34	46,6
	Palbociclib&Ribociclib	4	5.5
	Ribociclib	35	47.9
Liver metastasis			
	Yes	22	30.1
	No	51	69.9
Hepatosteatosis			
	Grade 1	15	20.5
	Grade 2	12	16,4
	No	46	63.0
HbsAg			
	Negative	70	95.9
	Positive	3	4,1
Anti-Hbs			
	Negative	44	60.3
	Positive	29	39.7
Anti-HCV			
	Negative	71	97.3
	Positive	2	2,7
Anti-Hbc IgG			
	Negative	57	78.1
	Positive	16	21.9
De novo Metastasis			
	Yes	44	60.3
	No	29	39.7
Anthracycline and Taxane Use			
	No	31	42,5
	Yes	42	57.5
Comorbidity*			
	No	37	50.7
	Yes	36	49.3
Additional drug use			
	No	3	4,1
	Yes	70	95.9
Neutropenia in Follow-up			
	Yes	51	69.9
	No	22	30.1
Hepatotoxicity			
	Yes	25	34,2
	No	48	65.8

* Diabetes, hypertension, hyperlipidemia, asthma

Table 2
Laboratory data of patients

	Mean±SD	Median (Min-Max)
Estrogen receptor (%)	85.6±17.2	90 (0-100)
Progesterone receptor (%)	49.8±38.3	60 (0-100)
Ki-67 (%)	20.6±15.7	20 (1-70)
Time from cytotoxic chemotherapy to CDK* 4/6 inhibitor (months)	22,5±30.3	10 (0-120)
Aspartate aminotrasferase (U/L)	324,3±724,9	62 (17-2656)
Alanine aminotransferase (U/L)	190.6±241.9	95 (14-912)
Total bilirubin (mg/dL)	6,55±4,4	5.2 (2,3-12,4)
Direct bilirubin (mg/dL)	3.5±2,37	2,85 (1.1-6,8)

* cyclin-dependent kinase

Table 3
Demographic data of patients with and without hepatotoxicity

		Patients with hepatotoxicity	Patients without hepatotoxicity	p-value
Sex	Male	23 (29.5)	45 (70.5)	0.770
	Female	2 (40)	3 (60)	
Palbosilib/Ribocilib	Palbociclib	11 (32.3)	23 (67.7)	0.845
	Palbociclib&Ribociclib	1 (25)	3 (75)	
	Ribociclib	13 (37.1)	22 (62.9)	
Liver metastasis	Yes	12 (54,5)	10 (45.5)	0.016
	No	13 (25.4)	38 (74,6)	
Hepatosteatosis	Grade 1	6 (40)	9 (60)	0.667
	Grade 2	5 (41.6)	7 (58,4)	
	No	14 (30.4)	32 (69.6)	
HbsAg	Negative	24 (34,2)	46 (65.8)	0.973
	Positive	1 (33,3)	2 (66,7)	
Anti-Hbs	Negative	16 (36.3)	28 (63,7)	0.639
	Positive	9 (31)	20 (69)	
Anti-Hcv	Negative	24 (3,8)	47 (66.2)	0.634
	Positive	1 (50)	1 (50)	
Anti-Hbc IgG	Negative	18 (31.6)	39 (68.4)	0.365
	Positive	7 (43,7)	9 (56.3)	
De novo Metastasis	Yes	14 (31.8)	30 (68.2)	0.590
	No	11 (37.9)	18 (62.1)	
Anthracycline and Taxane Use	No	10 (32.2)	21 (67.8)	0.758
	Yes	15 (35.7)	27 (64,3)	
Chemotherapy in the Meta-static Stage	Yes	17 (47.2)	19 (52.8)	0.021
	No	8 (21.6)	29 (78.4)	
Comorbidity*	No	15 (40.5)	22 (59.5)	0.251
	Yes	10 (27.7)	26 (72.3)	
Additional Drug Use	No	24 (34,2)	46 (65.8)	0.973
	Yes	1 (33,3)	2 (66.7)	
Neutropenia	Yes	19 (37.2)	32 (62.8)	0.410
	No	6 (27.3)	16 (72.7)	

* Diabetes, hypertension, hyperlipidemia, asthma

Table 4
Laboratory data of patients with and without hepatotoxicity

	Patients with hepatotoxicity	Patients without hepatotoxicity	p-value
Estrogen receptor (%)	88.4±20.9 90 (0-100)	83,9±14,7 90 (40-100)	0.336
Progesterone receptor (%)	56.5±35.3 62.5 (0-100)	45.9±39.9 55 (0-100)	0.308
Ki-67 (%)	19.9±10.6 20 (2-40)	20.9±8.0 15 (1-70)	0.823
Time from cytotoxic chemotherapy to CDK* 4/6 inhibitor (months)	11.9±3,1 8 (0-52)	28.2±35.2 11 (0-120)	0.046
Aspartate aminotrasferase (U/L)	327.2±739.7 62 (17-2656)	252±0.0 252 (252-252)	0.921
Alanine aminotransferase (U/L)	182.0±243,1 92.5 (14-912)	397±0.0 397 (397-397)	0.395
Total bilirubin (mg/dl)	6.55±4,4 5.2 (2.3-12.4)	-	NA
Direct bilirubin (mg/dl)	3,5±2.3 2.85 (1.1-6.8)	-	NA

* cyclin-dependent kinase

-ments for hormone receptor-positive and HER2-negative patients continues[11].

Finally, CDK 4/6 inhibitors have been used in combination with hormone therapies in this group of patients, which increased survival rates.

Ribociclib, palbociclib, and abemaciclib are CDK 4/6 inhibitors that are in use at present. With the introduction of these drugs, PFS for metastatic breast cancer patients increased from 6.1 to 24.8 months[12], while OS increased from 15.4 months to 53.7 months[13]. Side effects associated with these drugs vary depending on the

affinity of the drugs to different CDKs. While the most common side effect of ribociclib and palbociclib is neutropenia, diarrhea has been reported as the most common side effect associated with abemaciclib[6,8,9].

The incidence of hepatotoxicity seems to be higher in patients using ribociclib than in patients using the other drugs. These patients should be followed up with ALT and AST values. The median time to severe hepatotoxicity (≥ grade 3) is 85 days, regardless of the endocrine therapy used with ribociclib, and the median time to resolution to ≤ grade 2 is 22 days after the discontinuation of the drug[14]. ALT and AST values rapidly increase to critical levels in patients who are reinitiated on ribociclib[15].

In our study, 32.3% of the patients receiving palbociclib and 37.1% of the patients receiving ribociclib developed hepatotoxicity (p=0.676). While grade 3-4 ALT elevation was observed in 5 (14.2%) patients among those receiving ribociclib, grade 3-4 ALT elevation was observed in 2 (5.8%) patients among those receiving palbociclib (p=0.226). The MONALEESA 2-3-7 studies evaluating the efficacy and side effects of ribociclib showed grade 3-4 ALT elevations in 9.3%, 8.5%, and 5% of patients, respectively, while the PALOMA 3 study evaluating the efficacy and side effects of palbociclib found grade 3-4 ALT elevation in 2% of patients16. In our study, all patients with grade 3-4 ALT elevations had liver metastases. On the other hand, 12 (54.5%) of the patients with liver metastasis developed ALT elevation, while 7 (58.3%) of them developed grade 3-4 ALT elevation. This result shows that liver metastasis can increase hepatotoxicity and that these drugs should be preferred more carefully in the group of patients with liver metastasis. Since the phase studies of CDK 4/6 inhibitors did not indicate whether the patients with hepatotoxicity had liver metastases, we are of the opinion that this should be clarified with a subgroup analysis.

Of the 73 patients included in the study, 46 (63.0%) had an abdominal ultrasound report that met the criteria. Six of the 7 patients who were treated with ribociclib or palbociclib and had grade 3-4 hepatotoxicity had an abdominal ultrasound imaging. While 1 patient who received ribociclib with grade 3 hepatotoxicity had grade 2 hepatic steatosis, the other 5 patients did not have hepatic steatosis. Since there was only one patient with hepatic steatosis, it could not be speculated on whether hepatic steatosis triggered hepatotoxicity.

The evaluation of the comorbid diseases of 7 patients with grade 3-4 hepatotoxicity revealed that 1 patient had diabetes mellitus and 1 patient had hypertension, both of whom were on palbociclib. Five patients who had grade 3-4 ALT elevation and were on ribociclib had no comorbid disease. It can be stated that ribociclib is more toxic to the liver than palbociclib, since patients who received ribociclib and developed grade 3-4 hepatotoxicity had no disease that facilitates hepatotoxicity.The evaluation of the same 7 patients with grade 3-4 hepatotoxicity unveiled that 2 (100%) patients with palbociclib-induced hepatotoxicity had increased total and direct bilirubin values (total bilirubin 11.6-12.4), while 2 (40%) of 5 patients using ribociclib had increased levels of total and direct bilirubin (total bilirubin 5.9-6.4). Although the rate of hepatotoxicity was higher with ribociclib

than with palbociclib, the rate of elevated levels of bilirubin was observed to be higher in the palbociclib group. It has been shown in the literature that hepatotoxicity does not develop with the other drug when switching between CDK 4/6 inhibitors due to hepatotoxicity. This suggests that the hepatotoxicity mechanism of these two drugs may be different[16,17].

With regard to neutropenia side effect, 7 (20.5%) of the patients using palbociclib and 13 (37.1%) of the patients using ribociclib developed grade 3-4 neutropenia. While 2 patients who received palbociclib and developed grade 3-4 hepatotoxicity had grade 3-4 neutropenia (100%), 2 of the 5 patients who received ribociclib and developed grade 3-4 hepatotoxicity had grade 3-4 neutropenia (40%). This suggests that these two toxicities may develop concurrently in patients receiving palbociclib, and when one develops, the patient should be followed up closely for the other toxicity.

Of the 25 patients who developed hepatotoxicity of any grade while using ribociclib or palbociclib, 1 were HBsAg-positive and 8 were antiHBs and antiHBc IgG positive. One of the 5 patients with ribociclib-induced grade 3-4 toxicity and 1 of the 2 patients with palbociclib-induced grade 3-4 toxicity was anti-HBc IgG-positive. All patients who were positive for anti-HBc IgG were initiated on prophylactic treatment for hepatitis.

5. Conclusions

In conclusion, the severity of hepatotoxicity may require discontinuation of treatment in a limited number of patients. It can be stated that ribociclib is more toxic to the liver than palbociclib, since patients who received ribociclib and developed grade 3-4 hepatotoxicity had no disease that facilitates hepatotoxicity. We believe that more comprehensive studies are needed on this issue to determine the factors that facilitate hepatotoxicity such as liver metastasis and to select the drug accordingly will prevent patients from being devoid of this group of drugs and discontinuing their treatment due to toxicity.

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Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Adana City Training and Research Hospital Hospital Medical Ethics Committee with the decision no. 1473 dated 01.07.2021.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Serdar Ata, Filiz Araz, Timuçin Çil and Berna Bozkurt Duman. The first draft of the manuscript was written by Serdar Ata and all authors commented to previous versions of the manuscript. All authors read and approved the final manuscript.

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