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Evaluation of the relationship between toxicity of cyclin-dependent kinase 4/6 inhibitors and body surface area

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SUMMARY

OBJECTIVE: This study aimed to evaluate the relationship between the toxicity of cyclin-dependent kinase 4/6 inhibitors and body mass index and body surface area.

METHODS: A total of 83 patients were included in the study. Patients were divided into 4 groups as 18–24.9, 25–29.9, 30–39.9, and >40 kg/m^2 according to body mass index and into two groups as below and above 1.77 according to body surface area. The relationship between body mass index and body surface area and side effects was evaluated.

RESULTS: No statistically significant difference was found between body mass index groups and side effects. Grade 3 neutropenia was more common in patients on palbociclib with a body surface area≤1.77. In our study, it was revealed that less hematological side effects can be encountered when body surface area is taken into account.

KEYWORDS: Breast cancer. Drug toxicity. Body measures. Toxicity.

INTRODUCTION

Breast cancer is the most common cancer in women and the most common cause of death[1]. In patients with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer, treatment is initiated with a combination of cyclin-dependent kinase (CDK) 4/6 inhibitors plus endocrine therapy if the visceral crisis is not considered[2]. CDK4 and CDK6 form a complex with cyclin D, leading to phosphorylation of retinoblastoma (Rb) and activation of E2F. Rb phosphorylation is prevented by CDK4/6 inhibition. Inactivated E2F prevents the transition from G1 to S phase and decreases cell proliferation[3].

Apart from cell cycle regulation, the cyclin-CDK-Rb-E2F pathway also contributes to important metabolic processes such as lipid synthesis, insulin secretion, and glucose production[4]. Some studies have found an association between CDK4 deficiency with impaired lipogenesis and increased lipolysis[5,6]. Preclinical studies have found that CDK inhibitor therapies increase lipid utilization during a high-fat diet and that CDK4/6 inhibitors may be potential targets in the treatment of obesity[7]. CDK4/6 inhibitors affect body fat and muscle mass.

It is known that weight gain and obesity are associated with a worse prognosis in HR-positive early-stage breast cancer[8,9]. However, there are insufficient data on the effects of BMI in metastatic patients. All metastatic patients start treatment with CDK4/6 inhibitors at the same dose. In our study, we aimed to evaluate the relationship between the toxicity of CDK4/6 inhibitors and body mass index (BMI) and body surface area (BSA).

METHODS

This study included 87 patients with metastatic HR-positive breast cancer who received CDK4/6 inhibitor (ribociclib 1×600 mg or palbociclib 1×125 mg) and endocrine therapy (fulvestrant or aromatase inhibitor) between January 2022 and July 2022 and was followed up in our clinic between January 2022 and July 2022 and used these treatments for at least 3 months. Four patients whose data could not be reached and who were followed up in other centers were excluded from the study. Patients were divided into 4 groups as 18–24.9, 25–29.9, 30–39.9, and >40 kg/m^2 according to BMI and into two groups as below and above 1.77 according to BSA. The study was conducted following the Helsinki Declaration of 1975, revised in 2000. Data use permission and ethics committee approval were obtained from relevant institutions.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social

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Sciences, IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as n and % for categorical variables and mean±SD and median (IQR) for continuous variables. The drug-related toxicities of the patients were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) guideline. The chi-square test or Fisher's exact test was used to compare categorical variables. $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the patients included in the study was 51.29±12.65 years. BMI, BSA, treatments, mortality, and progression status of the patients are shown in Table 1.

Table 1. Distribution of body mass index, body surface area, and clinical variables of patients.

	n	%
Body mass index, n (%)		
18–24.9	19	22.9
25–29.9	26	31.3
30–39.9	32	38.6
40–60	6	7.2
Body surface area, n (%)		
1.77 or less	43	51.8
1.77 over	40	48.2
Medicines, n (%)		
Ribociclib	62	74.7
Palbociclib	21	25.3
Previous endocrinology treatment, n (%)		
Exist	45	54.2
None	38	45.8
Neoadjuvant or adjuvant treatment, n (%)		
Exist	32	38.6
None	51	61.4
Mortality, n (%)		
Right	73	88.0
Ex	10	12.0
Progression, n (%)		
None	62	75.6
Exist	20	24.4
	Mean±SD	**Median (IQR)**
Age	51.29±12.65	51.00 (19.00)
Body surface area	1.77±0.18	1.77 (0.29)
Follow-up time	67.58±61.44	45.46 (79.73)

Of all patients, 56 (67.5%) had neutropenia and 11 (13.3%) had elevated LFTs. There was no statistically significant difference between BMI groups and side effects ($p>0.05$). When the patients receiving ribociclib or palbociclib were evaluated separately, no statistically significant difference was found between the BMI groups and side effects ($p>0.05$).

As seen in Table 2, no statistically significant difference was found between BSA groups and side effects ($p>0.05$). A statistically significant difference was found only between Grade 1 neutropenia and BSA groups ($p=0.021$). Grade 1 neutropenia was observed more frequently in those with BSA>1.77.

When evaluated separately, no statistically significant difference was found between BSA groups and side effects in ribociclib patients ($p>0.05$).

As observed in Table 3, there was no statistically significant difference between the BSA groups and side effects in palbociclib recipients ($p>0.05$). However, a statistically significant difference was found only between grade 3 neutropenia and BSA groups ($p=0.030$). Grade 3 neutropenia was observed more frequently in patients with a BSA≤1.77.

DISCUSSION

Area under the curve (AUC), the most important pharmacokinetic parameter in anticancer drug exposure, is affected by many factors such as drug dose, age, gender, height, weight, hereditary variations in drug-metabolizing enzymes, and drug clearance. There is a lot of interindividual variation in AUC following a single dose of a drug[10]. To minimize this interindividual variation, the BSA is calculated according to the height and weight of the patient, and the treatment dose is adjusted according to the surface area of the patient when starting chemotherapy for oncology patients. When starting CDK4/6 inhibitors plus endocrine therapy, each patient is given a standard dose of treatment without taking into account the weight and height of the patients.

ASCO's updated guidelines suggest that there is no difference in the toxicity of these targeted agents between underweight and overweight people and that FDA-approved prescribing information should be used in all patients, regardless of obesity status[11].

Studies have shown the superiority of these treatments over placebo plus ET independent of BMI and BSA. However, studies investigating the toxicity of CDK4/6 inhibitors according to BMI and BSA are very limited. In the subgroup analysis in the study in which the safety analysis of MONOLISA 2-3 and 7 was evaluated, it was observed that the patients had similar BMI, so toxicity analysis was not performed according to BMI[12].

Table 2. Comparison of side effects according to body surface area groups.

	Body surface area		p
	≤1.77	>1.77	
Neutropenia, n (%)			
None	14 (32.6)	13 (32.5)	0.995[a]
Exist	29 (67.4)	27 (67.5)	
GR1 neutropenia, n (%)			
None	38 (88.4)	27 (67.5)	**0.021[a]**
Exist	5 (11.6)	13 (32.5)	
GR2 neutropenia, n (%)			
None	43 (100)	40 (100)	–
Exist	–	–	
GR3 neutropenia, n (%)			
None	22 (51.2)	26 (65)	0.202[a]
Exist	21 (48.8)	14 (35)	
GR4 neutropenia, n (%)			
None	40 (93)	40 (100)	0.242[b]
Exist	3 (7)	0 (0)	
LFT, n (%)			
None	35 (81.4)	37 (92.5)	0.136[a]
Exist	8 (18.6)	3 (7.5)	
GR1 LFT, n (%)			
None	42 (97.7)	39 (97.5)	1.000[b]
Exist	1 (2.3)	1 (2.5)	
GR2 LFT, n (%)			
None	41 (95.3)	40 (100)	0.495[b]
Exist	2 (4.7)	0 (0)	
GR3 LFT, n (%)			
None	39 (90.7)	39 (97.5)	0.361[b]
Exist	4 (9.3)	1 (2.5)	
GR4 LFT, n (%)			
None	42 (97.7)	39 (97.5)	1.000[b]
Exist	1 (2.3)	1 (2.5)	
GFR decrease, n (%)			
None	39 (90.7)	37 (92.5)	1.000[b]
Exist	4 (9.3)	3 (7.5)	
Soft tissue infection, n (%)			
None	43 (100)	36 (90)	0.050[b]
Exist	0 (0)	4 (10)	
Other, n (%)			
None	40 (93)	35 (87.5)	0.473[b]
Exist	3 (7)	5 (12.5)	

[a]Pearson's chi-square test; [b]Fisher's exact test; p<0.05 statistically significant. Bold values indicate the cut-off values mentioned in the article.

Table 3. Comparison of side effects according to body surface area groups in palbociclib recipients.

Palbociclib	Body surface area		p
	≤1.77	>1.77	
Neutropenia, n (%)			
None	2 (18.2)	4 (40)	0.361[b]
Exist	9 (81.8)	6 (60)	
GR1 neutropenia, n (%)			
None	11 (100)	7 (70)	0.090[b]
Exist	0 (0)	3 (30)	
GR2 neutropenia, n (%)			
None	11 (100)	10 (100)	–
Exist	–	–	
GR3 neutropenia, n (%)			
None	2 (18.2)	7 (70)	**0.030[b]**
Exist	9 (81.8)	3 (30)	
GR4 neutropenia, n (%)			
None	11 (100)	10 (100)	–
Exist	–	–	
LFT, n (%)			
None	10 (90.9)	9 (90)	1.000[b]
Exist	1 (9.1)	1 (10)	
GR1 LFT, n (%)			
None	11 (100)	9 (90)	0.476[b]
Exist	0 (0)	1 (10)	
GR2 LFT, n (%)			
None	10 (90.9)	10 (100)	1.000[b]
Exist	1 (9.1)	0 (0)	
GR3 LFT, n (%)			
None	11 (100)	10 (100)	–
Exist	–	–	
GR4 LFT, n (%)			
None	11 (100)	10 (100)	–
Exist	–	–	
GFR decrease, n (%)			
None	9 (81.8)	9 (90)	1.000[b]
Exist	2 (18.2)	1 (10)	
Soft tissue infection, n (%)			
None	11 (100)	7 (70)	0.090[b]
Exist	0 (0)	3 (30)	
Other, n (%)			
None	11 (100)	8 (80)	0.214[b]
Exist	0 (0)	2 (20)	

[b]Fisher's exact test; p<0.05 statistically significant. Bold values indicate the cut-off values mentioned in the article.

In the pooled analysis of the MONARCH 2 and 3 studies, patients were divided into four categories according to BMI, and the primary endpoint was PFS and the secondary endpoints were response rate, side effects, and weight loss according to BMI. In this analysis, no difference was found between BMI and PFS, while overweight and obese patients had higher response rates and lower neutropenia[13]. In our study, we did not find any difference between BMI and development of toxicity.

However, as BMI alone is not a good indicator of body fat distribution and sarcopenia and BSA is less affected by body fat distribution and is a better indicator of metabolic mass, we reassessed all patients (palbociclib and ribociclib users) divided into two groups according to BSA. We found that grade 1 neutropenia was more common in patients with BSA>1.77. When we separately evaluated patients on palbociclib, we found more grade 3 neutropenia in those with a BSA≤1.77. A review of the literature shows that neutropenia is more common in patients receiving palbociclib than in those receiving ribociclib, but there are no data on the relationship with BSA[14]. As the patients were generally of similar height, it was the weight of the patients that largely determined the increase in BSA. Neutrophil levels may also increase as an inflammatory marker in overweight patients. This may cause less neutropenia to be observed in these patients. Therefore, we think that we observed more severe neutropenia, especially in patients with lower BSA.

In our study, no difference was observed in terms of impairment in LFT and other toxicities according to BSA and BMI.

We found that CDK4/6 inhibitors can be used with equal safety in all subgroups according to BMI, but it should be taken into consideration that grade 3 neutropenia may be observed more frequently in patients with BSA ≤ 1.77 who are on palbociclib. This study is important because it revealed that less hematological side effects can be encountered when BSA is considered. Other parameters are needed to assess body composition. This idea can be improved with further studies using these parameters and with a larger number of patients.

AUTHORS' CONTRIBUTIONS

ŞYD: Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. **EF**: Investigation, Supervision.

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