Original Article

The Efficacy and Safety of CDK 4/6 Inhibitors Plus Endocrine Therapy with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor-2-Negative Metastatic Breast Cancer Patients

Hormon Reseptörü-Pozitif, İnsan Epidermal Büyüme Faktörü Reseptörü-2-Negatif Metastatik Meme Kanseri Hastalarında CDK 4/6 İnhibitörleri ile Endokrin Tedavisinin Etkinliği ve Güvenliği

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ABSTRACT

Introduction: Combining cyclin-dependent kinases 4/6 inhibitors with endocrine therapy are indicated as first or second-line treatment for hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.We aimed to investigate the efficacy and safety of adding CDKIs to endocrine therapy in patients whose tumors might have differing degrees of endocrine sensitivity.

Materials and methods: Totally, 99 patients with HR+, HER2-, ABC who received CDK4/6 inhibitor and hormonotherapy were included.Clinicopathological features of patients and progression-free survival (PFS) and overall survival (OS) outcomes were analyzed.The toxicity, combine drugs and the factors that may predict survival were also evaluated.

Results: This study with a median age of 51 years (range;31-80).The molecular subtypes of the patients were as follows; 51 patients (51.5%) were in the luminal A group, and 48 patients (48.5%) were in the luminal B HER2- group. Before CDK 4/6 inhibitor therapy, visceral and non-visceral metastasis were seen in 48 and 46 patients, respectively.At the median follow-up time of 13.7 months (range:3-48 months), the median OS was 38.5 months, the median PFS was 5.2 months. Univariate analysis demonstrated that the choice of CDK 4/6 agent was significantly associated with PFS. 6-months PFS rate with ribociclib was 42.3%, in palbociclib, it was 63.6%, in abemaciclib it was NA (not aplicable) (p=0.01).Univariate analysis revealed that the luminal type of tumor (p=0.002), advanced stage disease at the initial diagnosis (p<0.001), and presence of visceral metastasis (p=0.006) were significant factors for OS.

Discussion: In this study we demonstrated that there is a survival benefit for all three agents and there is a significant difference especially between first and second-line usage.

Keywords: breast neoplasm, cyclin-dependent kinases, survival, safety

ÖZET

Giriş: Sikline bağımlı kinaz 4/6 inhibitörlerinin endokrin terapi ile birleştirilmesi, hormon reseptörü pozitif, HER2 negatif ilerlemiş veya metastatik meme kanseri için birinci veya ikinci basamak tedavi olarak endikedir. Tümörleri farklı derecelerde endokrin duyarlılığa sahip olabilecek hastalarda endokrin tedaviye CDKI'lerin eklenmesinin etkinliğini ve güvenliğini araştırmayı amaçladık.

Gereç ve yöntemler: CDK4/6 inhibitörü ve hormon tedavisi alan HR+, HER2-, ABC'li toplam 99 hasta dahil edildi. Hastaların klinikopatolojik özellikleri ve progresyonsuz (PFS) ve genel sağkalım (OS) sonuçları analiz edildi. Toksisite, kombine ilaçlar ve sağkalımı öngörebilecek faktörler de değerlendirildi.

Bulgular: Ortanca yaşı 51 (31-80) olan bu çalışmada hastaların moleküler alt tipleri şöyleydi; 51 hasta (%51,5) lümen A grubunda, 48 hasta (%48,5) lüminal B HER2-grubunda.CDK 4/6 inhibitör tedavisi

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öncesi sırasıyla 48 ve 46 hastada visseral ve visseral olmayan metastaz görüldü. Medyan 13,7 aylık takip süresinde (dağılım:3-48 ay) , medyan OS 38,5 aydı, medyan PFS 5.2 aydı. Tek değişkenli analiz, CDK 4/6 ajanı seçiminin PFS ile önemli ölçüde ilişkili olduğunu gösterdi. Ribosiklib ile 6 aylık PFS oranı %42,3, palbosiklib ile %63,6, abemaciclib ile NA idi (p=0,01). Tek değişkenli analiz tümörün lüminal tipi (p=0,002), ilk tanı anındaki ileri evre hastalık (p<0,001) ve visseral metastaz varlığının (p=0,006) OS için anlamlı faktörler olduğunu ortaya koydu.
Tartışma: Bu çalışmada, her üç ajan için de sağkalım yararı olduğunu ve özellikle birinci ve ikinci basamak kullanım arasında anlamlı bir fark olduğunu gösterdik.

Anahtar kelimeler: meme kanseri, siklin bağımlı kinazlar, sağkalım, güvenlik

Introduction

Hormone receptor (HR) positive, human epidermal growth factor receptor-2 (HER2)-negative advanced breast cancer (ABC) constitutes approximately 70% of all metastatic breast cancer (MBC) [1,2]. Although effective results are obtained with various endocrine treatment options, resistance to treatment develops after a certain period of time and disease progression is observed. Many molecular resistance mechanisms have been defined, and in recent years, the effectiveness of various treatment combinations in overcoming resistance through these mechanisms has been proven and it has been demonstrated that they show significant survival advantages [1,2]. For this purpose, agents such as aromatase inhibitors (AI), gonadotropin-releasing hormone analogues and cyclin-dependent kinase (CDK) 4/6 inhibitors, the efficacy of which has been proven by recent studies, in patients with HR+, HER2-, ABC, according to menopausal status. It is used alone or in combination as the main components of treatment [1,3-6].

CDK4/6 inhibitors are rapidly transforming this treatment landscape for these patients. There are currently three CDK4/6 inhibitors that have been approved by the US Food and Drug Administration (FDA): palbociclib, ribociclib, and abemaciclib. All three CDK 4/6 inhibitors have been studied in combination with a non-steroidal aromatase inhibitor in the first-line setting. They have shown similar progression-free survival (PFS) contribution, but only ribociclib and abemaciclib provided overall survival (OS) benefit [4-6]. Moreover, they have also been studied in combination with the selective estrogen-receptor degrader fulvestrant in the first and second-line setting (7-9). PALOMA-3 with palbociclib, MONELESSA-3 with ribociclib, and MONARCH-2 with abemaciclib are all three conducted phase III studies. although there are some key study population differences between the phase III trials, these combination studies demonstrated significant improvement in PFS which is primary end point of them [7-9].

The aim of our study was to provide a real-life analysis of the efficacy and safety of CDK 4/6 inhibitors and combination patterns reported in HR+, HER2- for patients with ABC in the first and second-line setting.

Patients and Methods

In this study, a total of 99 patients with HR+, HER2-, ABC who were treated between 2018 and 2022 were retrospectively analyzed. Our study was conducted in accordance with the Declaration of Helsinki. The Local Ethics Committee of Istanbul Medipol University approved the study on January 2023 with E-10840098-772.02-269 decision number.

The data include demographic characteristics of patients, menopausal status, histo-pathology, stage of diagnosis, visceral metastasis, molecular characteristics of breast cancer, as well as adjuvant chemotherapy or endocrine therapy for operated patients. The CDK4/6 inhibitor used as treatment, combined drugs, side effects and toxicity secondary to treatment, objective response rate (ORR), OS and PFS were evaluated and recorded. Eastern Cooperative Oncology Group (ECOG) performance score (PS) was

used for the detection of performance status [10].

The response to treatment of all three CDK4-6 was assessed by thorax CT scan and abdomino-pelvic CT scan. It was evaluated with the Response Evaluation Criteria in Tumors (RECIST) version 1.1. A complete response (CR) was defined as the disappearance of all measurable disease, a partial response (PR) represented a decrease of at least 30% of the tumor volume and stable disease (SD) defined small changes that do not meet above criteria without actual progression of disease. Progressive disease (PD) was defined as more than 20% increase in tumor volume or any new sites of disease.

Statistical analysis

IBM SPSS Statistics for Windows (Version 20.0. Armonk, NY: IBM Corp IBM Corp. Released 2011) was used for statistical analysis. Parameters were described with their median values. Response rates and toxicity profiles according to CDK 4-6 inhibitor treatment choice were compared using the chi-squared test and Fisher's exact test. OS was defined as the time from diagnosis to the date of the patient's death. PFS was defined as the time from the diagnosis of advanced-stage disease to progression. Survival analysis and curves were established using the Kaplan-Meier method and compared with the long-rank test. Univariate analyses were carried out to assess the significant prognostic factors on survival. These significant prognostic factors were further analyzed by multivariate Cox regression in order to determine independent prognostic factors on survival. The 95% confidence interval [CI] was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in tests, and p values less than or equal to 0.05 were accepted to be statistically significant.

Results

Fifty-three of the patients were premeno-pausal, and 46 were postmenopausal with a median age of 51 years (range; 31-80). Disease recurrence <12 months after adjuvant treatment occurred in 25 patients. Before CDK 4/6 inhibitor therapy, visceral and non-visceral metastasis were seen in 48 and 46 patients, respectively. 47.5% of patients were treated with CDK 4/6 inhibitor in the first-line setting, 49.5% were in the second-line, and 3% were in the later-line setting. The rate of treatment-related toxicity was 64.7%, and grade 3 or higher toxicity was 26.3%. The CDK 4/6 agent dose was adjusted in 33 patients concerning toxicity. No treatment-related death or discontinuation to CDK 4/6 inhibitor agent was observed. (Table 1)

CR was observed in 22 (34.9%) patients with ribociclib, 7 (23.3%) with palbociclib, and 1 (20%) with abemaciclib. ORR in ribociclib, palbociclib and abemaciclib groups were 66.7%, 63.3%, 100% respectively. The best response did not significantly differ between CDK 4/6 inhibitor agents. Any grade of toxicity and grade 3 or higher toxicity were detected in 47 (74.6%), 22 (73.3%), 5 (100%) and 20(31.7%), 15 (50.0%), 1(20%) in groups, respectively. There was no significant difference between toxicity rates. However, hematological toxicity rates were significantly higher in patients treated with palbociclib and ribociclib compared with abemaciclib (89.8% and 81.0% vs 20%) ($p<0.001$). The diarrhea rates were significantly higher in patients treated with abemaciclib ($p<0.001$). (Table 2)

At the median follow-up time of 13.7 months (range: 3-48 months), the median OS was 38.5 months and the median PFS was 5.2 months. Univariate analysis demonstrated that the choice of CDK 4/6 agent was significantly associated with PFS. 6-months PFS rate with ribociclib was 42.3%, in palbociclib, it was 63.6%, in abemaciclib, it was NA ($p=0.01$). (Figure 1) Age, disease recurrence <12 months after adjuvant therapy, menopausal status, ECOG PS, history of curative surgery, the treatment line of CDK 4/6 inhibitor therapy and luminal type of disease had no significant impact on PFS. In patients with non-visceral metastasis, the median PFS was 5.2 months with ribociclib; 12.2 months with palbociclib; not reached in abemaciclib ($p=0.06$). In patients with visceral metastasis,

Table 1. Patient and tumor characteristics

Characteristics	N=99	%
Age	median 51(range 31-80)	
Menopausal status		
Premenopausal	53	53.5
Postmenopausal	46	46.5
Advance Stage Disease at initial diagnosis	55	56.1
History of		
Curative surgery	54	54.5
Adjuvant endocrine treatment	52	52.5
Luminal A disease	51	51.5
Luminal B disease	48	48.5
Disease recurrence < 12 months after adjuvant treatment	25	25.3
Metastatic site		
Non-visceral metastasis	46	46.5
Visceral metastasis	48	48.5
CDK 4-6 inhibitor		
1st line	47	47.5
2nd line	49	49.5
≥ 3rd line	3	3
Choice of CDK 4-6 inhibitor		
Ribociclib	63	63.6
Palbociclib	30	30.3
Abemaciclib	6	6.1
Choice of antiestrogen treatment		
Letrozole	54	54.5
Fulvestrant	45	45.5
Any Grade of toxicity with CDK 4-6 inh.	64	64.7
Grade 3 or higher toxicity	26	26.3
Dose adjustment due to toxicity	33	(33.3)

*CDK: cyclin-dependent kinases

Table 2: Response rates and toxicity profile according to the choice of CDK 4-6 inhibitor treatment

Characteristics	Ribociclib N (%)	Palbociclib N(%)	Abemaciclib N(%)	P
RECIST 1.1				
Complete response	22 (34.9)	7 (23.3)	1 (20.0)	
Partially response	20 (31.7)	12 (40.0)	4 (80.0)	
Stable Disease	3 (4.8)	3 (10.0)	0	0.4
Progressive Disease	18 (28.6)	8 (26.7)	0	
ORR	42 (66.7)	19 (63.3)	5 (100)	0.2
Any grade of toxicity	47 (74.6)	22 (73.3)	5 (100)	0.4
Grade ≥3 toxicity	20 (31.7)	15 (50.0)	1 (20.0)	0.1
Toxicity				
Hematological toxicity	35 (89.8)	17 (81.0)	1 (20.0)	
Liver toxicity	2 (5.1)	1 (4.8)	0	<0.001*
Cardiac toxicity	1 (2.6)	0	1 (20.0)	
Diarrhea	0	1 (4.8)	3 (60.0)	
Other	1 (2.6)	2 (9.5)	0	
Toxicity-related dose adjustment	22 (50.0)	12 (57.1)	1 (20.0)	0.24

ORR: Objective response rate
* p values <0.05 was regarded statistically significant."

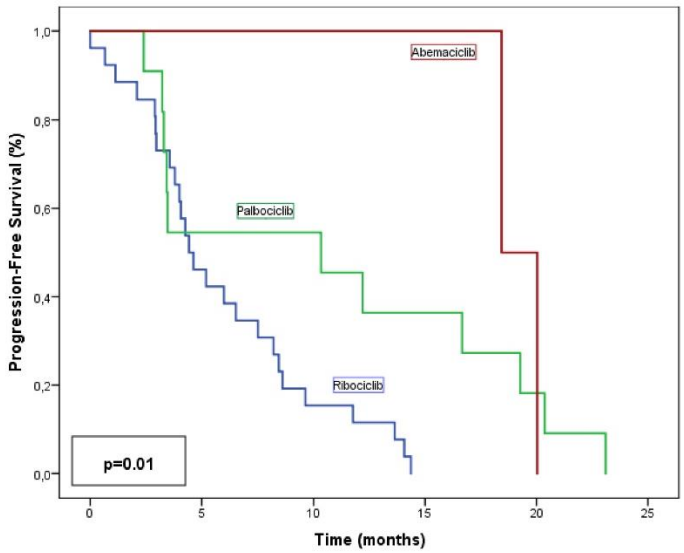

Figure 1. PFS according to CDK

Table 3. Prognostic factors for overall and progression-free survival

	PFS		OS	
Factor	Univariate analysis (p)	Multivariate analysis p (HR 95%CI)	Univariate analysis (p)	Multivariate analysis p (HR 95%CI)
Age (median 51 years)	0.9		0.8	
Performance status 0/1 vs. 2	0.2		0.3	
Menopausal status Premenopausal vs postmenopausal	0.2	0.7	0.1	
Advanced stage at initial diagnosis Yes vs. no	<0.001	0.9	0.5	0.7
Metastatic site (visceral vs. non-visceral)	0.006	0.03 (14.2; 1.25-16.6)	0.7	0.5
History of curative surgery Present vs. absent	0.9		0.7	0.5
Luminal A vs Luminal B	0.002	0.09	0.5	0.4
CDK 4-6 inhibitor in 1st line vs. later lines	0.002	0.05 (13,5; 1.02-17.7)	0.1	0.3
Choice of CDK 4-6 inhibitor agent	0.3	0.1	0.01	0.02 (0.2; 0.06-0.80)
Disease recurrence < 12 months after adjuvant treatment Yes vs. no	0.6	0.2	0.4	0.6

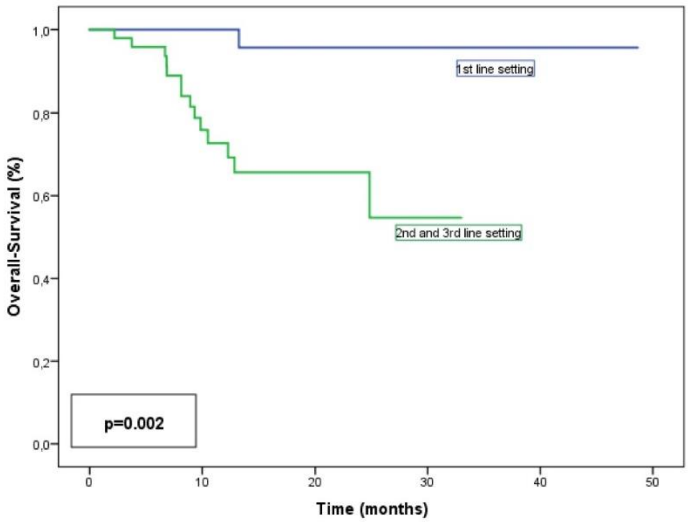

Figure 2. OS acording to CDK line

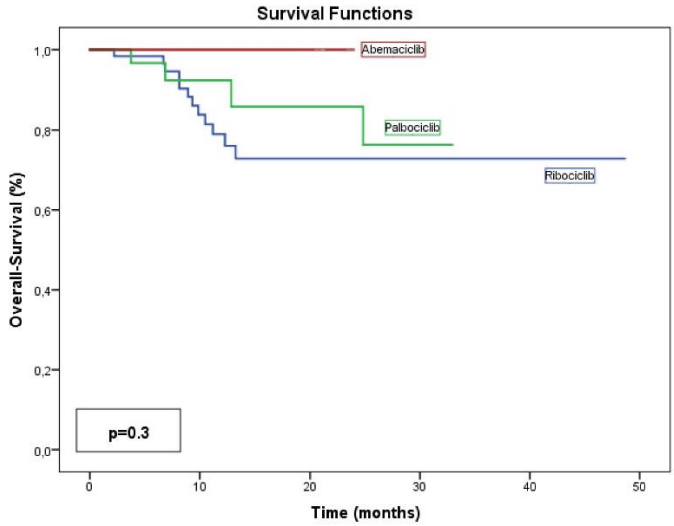

Figure 3. OS according to CDK

median PFS was 4.2 months with ribociclib, 3.3 months with palbociclib, and 18.4 months with abemaciclib (p=0.1). (Table 3)

The choice of CDK 4/6 inhibitor in first-line and later-line setting had a significant impact on PFS (p=0.002). 24-months OS rates were 95.7% vs 64.5%, respectively. (Figure 2)

Univariate analysis revealed that the luminal type of tumor (p=0.002), advanced stage disease at the initial diagnosis (p<0.001), and the presence of visceral metastasis (p=0.006) were significant factors for OS. There was no significant correlation between OS and CDK 4/6 inhibitor agent, disease recurrence <12 months after adjuvant therapy, menopausal status, EGOG PS and history of curative surgery. 24-months OS rate with ribociclib was 72.9%, in palbociclib it was 85.9%, in abemaciclib it was NR. (Figure 3)

Multivariate analysis was performed to identify independent prognostic factors for survival. It demonstrated that the choice of CDK 4/6 inhibitor agent was a significant independent prognostic factor for PFS (p=0.02, HR:0.2 95% CI 0.06-0.80). On the

other hand, metastatic site of disease (visceral vs non-visceral) and the line of CDK 4/6 inhibitor therapy (first-line vs later-lines) were independent prognostic factors for OS (p=0.03, HR:14.295% CI; 1.25-16.6; p=0.05, HR:13.5 95% CI 1.02-17.7, respectively).

Discussion

The development of CDK 4/6 inhibitors such as abemaciclib, palbociclib and ribociclib has changed the therapeutic approach in patients with HR+, HER2- MBC. The combination of these drugs with aromatase inhibitor and fulvestrant has been approved by all health authorities. Although there is no clinical study comparing all three agents, there are meta-analyzes in the literature where they are indirectly compared [11]. In this study, we evaluated the efficacy differences between the addition of each of the three CDK 4/6 inhibitors to the endocrine treatment according to PFS, OS, toxicity, and visceral involvement in patients with HR+, HER2-, ABC, treated and followed-up in our center. CDK 4/6 inhibitors were used in combination with NSAI (anastrozole/letrozole) in the first-line and received FDA approval. Phase III studies were conducted for PALOMA-2 for palbociclib, MONELESSA-2 for ribociclib, and MONARCH-3 for abemaciclib, all showing PFS contribution [4-6]. In conclusion, the choice of CDK 4/6 inhibitor agents in HR+, HER2-, ABC depends on several factors such as patient preference, comorbidities and disease burden. Although there is a difference in survivals between agents, it is not sufficient to influence our choice of treatment. Despite our limitations, in this study we demonstrated that there is a survival benefit for all three agents and there is a significant difference especially between first and second-line usage. In the future, studies including real-life analysis are needed in which all three CDK 4/6 inhibitors with more patients are compared in both first- and second-line setting.

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