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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Pan-Immune-Inflammation Value Predicts the Survival of Patients with ER-positive, HER-2-Negative Metastatic Breast Cancer Treated with CDK4/6 inhibitors

Pan-İmmün-İnflamasyon Değeri CDK4/6 İnhibitörleri ile Tedavi Edilen ER-Pozitif, HER-2-Negatif Metastatik Meme Kanseri Hastalarında Genel Sağkalımı Etkiler

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ABSTRACT

Aim: To define the prognostic value of pan immune-inflammation value (PIV) in patients with estrogen receptor (ER) positive, Human epidermal growth factor receptor-2 (HER-2) negative metastatic breast cancer receiving cyclin-dependent kinase 4/6 (CDK4/6) inhibitors.

Material and Method: The present study enrolled patients diagnosed with HR-positive, HER-2 negative metastatic breast cancer who were treated with novel CDK4/6 inhibitors palbociclib or ribociclib at Suleyman Demirel University Hospital, Turkey, and Antalya Hospital of Health Sciences University, Turkey from 2015 to 2020. The cut-off value of c-reactive protein albumin ratio (CRP/alb), neutrophil lymphocyte ratio (N/L), lymphocyte monocyte ratio(L/M), platelet lymphocyte ratio (Plt/L), systemic immune-inflammation index (SII), and PIV is determined by using the receiver operating characteristic (ROC) analysis. Progression-free survival (PFS) comparisons of palbociclib and ribociclib treatments, and CRP/alb, N/L, SII, and PIV were performed using Kaplan-Meier curves and median survival times. PIV was calculated as neutrophil x platelet x monocyte /lymphocyte count (10^9/L).

Results: Ninety-one patients were included in this study. The patients' mean age was 58.4±11.7 years. At a median follow-up of 48 months, 11% (10) of patients died. 53.8% (49) of patients had the metastatic disease when they were diagnosed. 87.9% (80) were postmenopausal, and 39.6% (36) received ribociclib, 60.4% (55) palbociclib. The cut-off value of PIV is calculated as 476.5 using the receiver operating characteristic (ROC) analysis. The Cox regression analysis for PFS showed that PIV (HR:4.68; p=0.022) and drugs combined with CDK4/6 (HR:4.68; p=0.022) were the only independent prognostic markers for PFS. Median progression-free difference was not significantly significant between ribociclib and palbociclib groups (27.9 vs 25.5 months respectively; %95 CI, 25.9-29; p=0.654).

Conclusions: PIV is a simple and inexpensive, easily calculated marker to predict the survival of patients with ER-positive, HER-2-negative metastatic breast cancer. This technique can assist physicians in putting tailored and focused treatment plans in place. Between ribociclib and palbociclib, there is no statistically significant difference in PFS.

Keywords: Pan immune-inflammation value, breast cancer, ribociclib, palbociclib

ÖZ

Amaç: Pan immün-inflamasyon değerinin (PIV) sikline bağımlı kinaz 4/6 (CDK4/6) inhibitörleri alan östrojen reseptörü (ER) pozitif , İnsan epidermal büyüme faktörü reseptörü-2 (HER-2) negatif olan metastatik meme kanseri hastalarında prognostik değerini tanımlamak.

Gereç ve Yöntem: Çalışmaya 2015-2020 yılları arasında Türkiye Süleyman Demirel ve Antalya Sağlık Bilimleri Üniversitesi Hastanesi'nde CDK4/6 inhibitörleri palbociclib veya ribociclib ile tedavi edilen hormon reseptörü (HR) pozitif HER-2 negatif metastatik meme kanseri tanılı hastalar dahil edildi. C-reaktif protein albümin (CRP/alb), nötrofil lenfosit (N/L), lenfosit monosit (L/M), trombosit lenfosit oranı (Plt/L), sistemik immün inflamasyon indeks (SII) ve PIV sınır değerleri, alıcı işletim karakteristik (ROC) analizi kullanılarak belirlendi. Palbosiklib ve ribosiklib tedavileri ile CRP/alb, N/L, SII ve PIV değerlerinin progresyonsuz sağkalım (PFS) açısından karşılaştırmaları, Kaplan-Meier eğrileri ve medyan sağkalım süreleri kullanılarak yapıldı. PIV değeri nötrofil x trombosit x monosit /lenfosit sayısı (109/L) olarak hesaplandı.

Bulgular: Bu çalışmaya 91 hasta dahil edildi. Yaş ortalaması 58.4±11.7 yıldı. Medyan 48 aylık takipte hastaların %11(10)'i hayatını kaybetti. Hastaların %53.8'i (49) metastatik evrede tanı aldı. Hastaların %87.9'i (80) postmenopozaldi, %39.6'u (36) ribociclib, %60.4'ü (55) palbociclib ile tedavi edildi. PIV'in sınır değeri ROC analizi kullanılarak 476.5 hesaplandı. PFS için yapılan COX regresyon analizinde PIV (HR:4.68;p=0.022) ve CDK4/6 ile kullanılan ilaç kombinasyonu (HR:2.66;p=0.006) PFS için bağımsız prognostik belirteçler olarak değerlendirildi. Ribosiklib ve palbosiklib hasta grupları arasındaki medyan PFS süreleri arasındaki fark istatistiksel olarak anlamlı bulunmadı (27.9'a karşı 25.5 ay; %95 CI,25.9-29;p=0.654).

Sonuç: PIV ER-pozitif, HER-2-negatif metastatik meme kanseri hastalarının sağkalımını predikte etmek için kullanılabilen basit, ucuz ve kolayca hesaplanabilen bir belirteçtir. Bu yöntem, klinisyenlere kişiye özel tedavi planı belirlemek için yardımcı olabilir. Ribociclib ve palbociclib tedavileri arasında PFS'yi belirlemek açısından istatistiksel olarak anlamlı bir fark bulunmadı.

Anahtar Kelimeler: Pan immün-inflamasyon değeri, meme kanseri, ribociclib, palbociclib

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INTRODUCTION

Breast cancer is the most common cancer with an annual rate of approximately 226,000 (11.7%) new cases. It is the most common cause of cancer-related death (15.5%) in women (1). Breast cancer can be broadly classified into three major groups based on the expression of the estrogen receptor (ER), the human epidermal growth factor receptor 2 (HER-2) (ER positive or negative), and the absence of both the ER and HER-2 receptors (triple negative), which can influence the biological decision regarding the course of treatment.

The most common biological subtype of metastatic breast cancer is the ER positive HER-2 negative subgroup. Cyclin-dependent kinases (CDK4 and CDK6), which control the cell cycle, are crucial for the growth and development of tumors. Particularly in breast cancer, where estrogen promotes tumor growth, this pathway is regarded to be the primary one for the genesis of cancer (2). Studies have been published in which three CDK4/6 inhibitors, ribociclib, palbociclib and abemaciclib developed in recent years contributed to overall survival in ER-positive HER-2-negative patients with metastatic breast cancer patients (3-5).

Chronic inflammation and cancer have a complex relationship that has been ssearched a lot; inflammation is now recognized as one of the characteristics that make this relationship possible. Utilizing plasma tumor biomarkers has the advantages of being, practical, and affordable (6). Sata et al. found a statistically significant relationship between, CRP, neutrophil, and lymphocyte count and overall survival of patients with metastatic breast cancer receiving eribulin (7). In addition to being a carrier protein, albumin also controls tissue repair, metabolism, and immunity of cells, when it is low, immune system activity weakens and tumor cachexia develops, and tumor prognosis worsens. In the study conducted by Liu, the high CRP/albumin ratio is related to worse disease-free survival and OS in patients with luminal B subtype breast cancer (8). Fuca proposed a new prognostic marker, calculated as neutrophil x platelet x monocyte/lymphocyte, pan-immune-inflammation value (PIV) for patients with metastatic colon cancer patients (9). PIV is studied as a prognostic marker for patients with breast cancer undergoing operation (10), receiving neoadjuvant chemotherapy (11), receiving first-line trastuzumab, pertuzumab, and docetaxel therapy (12), and at young age (13).

In this study we aimed to investigate the prognostic value of CRP/albumin, neutrophil/lymphocyte ratio, PIV, and define the PFS and OS in patients with HR-positive, HER-2 negative metastatic breast cancer receiving CDK4/6 inhibitors palbociclib and ribociclib followed up at medical oncology units of 2 centers in Turkey.

MATERIAL AND METHOD

The present study enrolled patients diagnosed with HR-positive, HER-2 negative metastatic breast cancer who were treated with novel CDK4/6 inhibitors palbociclib or ribociclib at Süleyman Demirel University Hospital, Turkey, and Antalya Hospital of Health Sciences University, Turkey from 2015 to 2020. Because the investigation was retrospective, there was no need for scientific research funding. Ninety-nine patients were identified, but eight were excluded from the study because they dropped out of follow-up. patients with metastatic breast cancer who were treated at the medical oncology clinic were assessed. All patients were over the age of 18, had follow-up and treatment in our unit, and had records that we could access. Patients' age, clinicopathological characteristics, laboratory results,co-morbid diseases, metastasis locations and numbers, treatments and laboratory results, last outpatient clinic control, and death dates were recorded retrospectively.

Statistically Analysis

Study data were analyzed using SPSS (Statistical Package for the Social Sciences) 23.0 and MedCalc 20.110. Numeric data are expressed as the median and interquartile range (IQR), and frequent data are expressed as rates. A comparison of the two groups with numeric data was performed using the Mann-Whitney U test. Pearson's chi-square and Fischer's exact tests were used to comparing the two groups with categorical variables.

Progression-free survival (PFS) comparisons of palbociclib and ribociclib treatments, and CRP/albumin, neutrophil/lymphocyte ratio, systemic immune inflammation index, and PIV were performed using Kaplan-Meier curves and median survival times. A comparison of the two groups in the Kaplan-Meier analysis was carried out using the log-rank test. Univariate and multivariate backward Cox regression analyses were used to establish hazard ratios with 95% confidence intervals for each variable. The cut-off value of CRP/alb, N/L, L/M, Plt/L, SII, and PIV is determined by using the receiver operating characteristic (ROC) analysis (**Table 1**)(**Figure 1**). The hypotheses were constructed as two-tailed, and an alpha value of 0.05 was accepted as significant.

Table 1. ROC curve analysis determining cut-off values

	AUC	SS	%95 CI	cut off	Sensitive (%)	Spesifite (%)
PIV	0,557	0,113	0,336-0779	476,50	40,00	60
SII	0,554	0,103	0,352-0,756	836,50	50,00	68,00
Crp/Alb	0,543	0,102	0,342-0,743	6,50	40,00	77,00
N/L	0,558	0,102	0,359-0,757	3,50	20,00	91,00
L/M	0,459	0,113	0,237-0,681	6,50	50,00	59,00
Plt/L	0,576	0,104	0,371-0,780	242,00	20,00	80,00

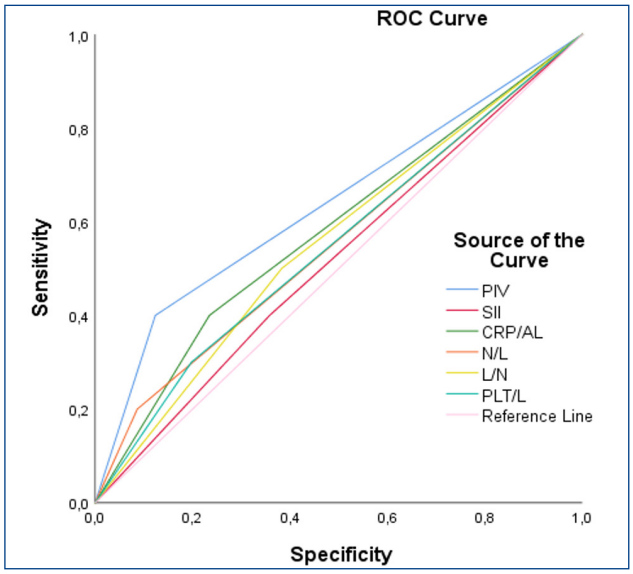

Figure 1. ROC curves defining the sensitivity and specificity of cut-off values

RESULTS

Ninety-one patients were included in this study. The patients' mean age was 58.4±11.7 years. At a median follow-up of 48 months, 11% (10) of patients died. 53.8% (49) of patients had the metastatic disease when they were diagnosed. 87.9% (80) were postmenopausal, and 39.6% (36) received ribociclib, 60.4% (55) palbociclib. The clinicopathological characteristics of patients, the other prognostic markers, and the comparison of PIV are shown in **Table 2**. PIV was statistically related to CDK4/6 (p=0.005), SII, N/L, L/M, and death (p<0.05).

The Cox regression analysis for PFS showed that PIV (HR:4.68; p=0.022) and drugs combined with CDK4/6 (HR:4.68; p=0.022) were only independent prognostic markers for PFS (**Table 3**).

Table 3. COX regression analysis for PFS

	PFS Univariate HR (95% CI for HR)			p
Age	1,746	0,436	6,985	0,431
Comorbidity	0,911	0,245	3,392	0,889
Diagnostic stage	1,623	0,665	3,960	0,287
PS	3,847	0,980	15,110	0,054
Menopause	0,899	0,112	7,188	0,920
CDK4/6	0,730	0,183	2,920	0,657
CDK4/6 combined	2,663	1,329	5,336	0,006
Metastasis	1,723	0,771	3,854	0,185
PIV	4,682	1,253	17,499	0,022
SII	1,443	0,387	5,377	0,585
CRP/Alb	2,296	0,616	8,556	0,216
N/L	3,000	0,605	14,866	0,179
L/M	1,250	0,335	4,657	0,740
Plt/L	1,983	0,495	7,955	0,334

Table 2. Comparison of clinicopathologic characteristics and PIV

	PIV				P
	<476,5		>476,5		
	N	%	N	%	
Age					0,093
<60	40	51,9	4	28,6	
>60	37	48,1	10	71,4	
Comorbidity					0,243
no	44	57,1	6	42,9	
yes	33	42,9	8	57,1	
Diagnostic Stage					0,083
1	3	3,9	0	0,0	
2	18	23,4	2	14,3	
3	18	23,4	1	7,1	
4	38	49,4	11	78,6	
PS					0,528
0	2	2,6	0	0,0	
1	67	87,0	12	85,7	
2	8	10,4	2	14,3	
Menopause					0,466
Postmenopausal	67	87,0	13	92,9	
Peri/premenopausal	10	13,0	1	7,1	
CDK 4/6					0,005
Ribociklib	35	45,5	1	7,1	
Palbociklib	42	54,5	13	92,9	
CDK4/6 combined					0,974
Letrozole	46	59,7	7	50,00	
Fulvestrant	24	31,2	7	50,00	
Exemestane	6	7,8	0	0,00	
Anastrozole	1	1,3	0	0,00	
Metastasis					0,340
Bone	23	29,9	8	57,1	
Visceral	17	22,1	0	0,0	
Bone+Visceral	37	48,1	5	35,7	
Bone+Bone marrow	0	0,0	1	7,1	
SII					0,001
<836,5	55	71,4	3	21,4	
>836,5	22	28,6	11	78,6	
CRP/Alb					0,252
<6,5	56	72,70	12	85,7	
>65	21	27,30	2	14,3	
N/L					0,004
<3,5	73	94,8	9	64,3	
>3,5	4	5,2	5	35,7	
L/M					0,000
<6,5	41	53,2	14	100,0	
>6,5	36	46,8	0	0,0	
Plt/L					0,400
<242	60	77,9	12	85,7	
>242	17	22,1	2	14,3	
Death					0,044
Alive	71	92,2	10	71,4	
Exitus	6	7,8	4	28,6	

PS performance score,SII systemic immune-inlammation index, N/L neutrophil-lymphocyte ratio,L/M lymphocyte-monocyte ratio,CRP/Alb c-reactive proteion-albumin ratio, Plt/L platelet-lymphocyte ratio,

In PIV high group the progression risk was 4.68 times higher than in the low group. In the fulvestrant group, the progression risk was 2.66 times higher than the letrozole or exemestane group.

Median PFS was 28.3 months in PIV low group and 22.1 in the high group; it was statistically significant (%95 CI,25.9-29; p=0.011) (**Figure 2**). Median PFS was 27.9 months with ribociclib and 25.5 with palbociclib, but it was not statistically significant (%95 CI,25.9-29;p=0.654) (**Figure 3**)

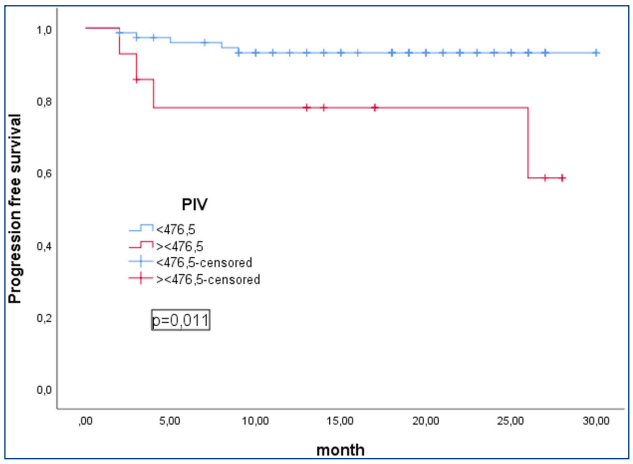

Figure 2. Kaplan-Meier curve representing PFS according to PIV low and high groups

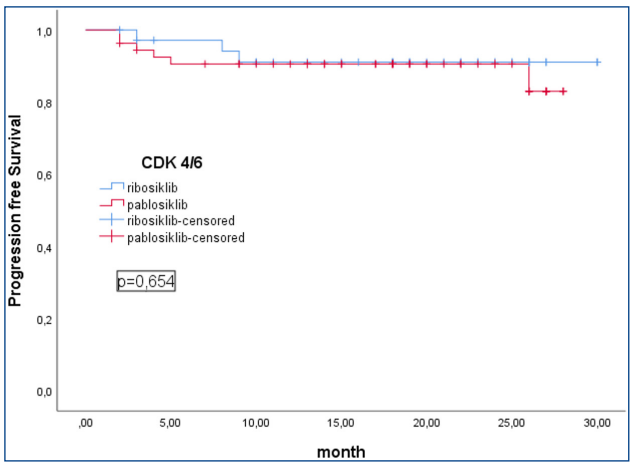

Figure 3. Kaplan-Meier curve representing PFS according to ribociclib and palbociclib

DISCUSSION

With the use of novel CDK4/6 inhibitors, the overall survival of patients with HR+, HER-2- metastatic breast cancer has increased to over 5 years (3, 4). Inflammatory cells play a significant role in the development of tumors and the prognosis of cancer patients, particularly when it comes to certain physiological responses to inflammation (14). The stability of the normal intracellular environment can be destroyed by inflammatory mediators, which promote aberrant cell growth and subsequent cell degeneration (15). Numerous cancers have been researched to determine the association between the ratio of neutrophils, lymphocytes, platelets, and monocytes in peripheral blood and the prognosis of patients with cancer. In a meta-analysis including 8563 patients with breast cancer, conducted by Ethier high NLR was associated with worse DFS and OS; however this effect was more prominent in ER -, HER-2- subtype (16).

Ma searched the prognostic value of NLR, PLR, and LMR in patients with metastatic breast cancer undergoing neoadjuvant chemotherapy, and found LMR as an independent prognostic marker (17).

We don't have enough prognostic markers to guide the therapy and predict the survival of patients. PIV is a novel and simple marker calculated with the blood parameters. In the current study, the results showed that PIV was an independent prognostic marker for patients with HR+, HER-2 – metastatic breast cancer. Ligorio searched the prognostic impact of PIV in HER-2+ metastatic breast cancer undergoing trastuzumab, docetaxel, and pertuzumab therapy. High PIV was an independent prognostic factor for worse OS (12).

Sahin searched the prognostic value of PIV in patients undergoing neoadjuvant chemotherapy with metastatic breast cancer (11). Demir searched the prognostic impact of PIV in young patients with breast cancer. High PIV was associated with worse OS in their study but it was not statistically significant (13). Our study is the first to search the prognostic impact of PIV in patients with metastatic ER+, HER-2- breast cancer receiving CDK4/6 inhibitors. The calculation of PIV is simple and inexpensive. Therefore it is a useful marker to predict the prognosis in this group of patients.

The second end-point of this study is to define the PFS in months with ribociclib and palbociclib. The median PFS was 27.9 months with ribociclib and 25.5 with palbociclib. This result is consistent with the MONALEESA-2 and PALOMA-2 clinical trials (3, 4).

Our study's limitations include the relatively small number of patients analyzed, the retrospective character of the research, and the brief follow-up period.

CONCLUSION

PIV is a simple and inexpensive, easily calculated marker to predict the survival of patients with ER-positive, HER-2-negative metastatic breast cancer. This technique can assist physicians in putting tailored and focused treatment plans in place. Between ribociclib and palbociclib, there is no statistically significant difference in PFS.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study is approved by Ethics Comittee of Süleyman Demirel University with id 17.08.2022/224.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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