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Research Article

Is Clinical Risk Score a Useful Predictive Marker of Early Recurrence Among Metastatic Breast Cancer Patients Treated with CDK4/6 Inhibitors?

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Abstract

Objectives: The addition of CDK4/6 inhibitors to standard hormonotherapy improved progression-free survival(PFS) of hormone-positive, HER-2 negative metastatic breast cancer(mBC). We analyzed clinicopathological risk factors predicting early recurrence in mBC patients treated with a combination of CDK4/6 inhibitor and hormonotherapy.

Methods: 229 patients were included, and 95 recurrences were seen. Median ER and PR expressions, ki67 levels, metastatic sites, number of metastasis, and grade were related to recurrence. Patients were classified according to the presence of prognostic factors: group 1 included patients with 0-1 risk factors, group 2 with 2-3 risk factors, and group 3 with ≥4risk factors.

Results: Median ER, PR, and ki67 levels were 90, 60, and 25,respectively. Median ER, PR, Kİ67, grade, metastatic site, and the number of metastasis were related to PFS. Advanced CDK4/6 line and response were significant for PFS.Median PFS was 6.5 months for recurrent patients. According to the predictive model, patients who recurred before 6.5 months had a high-risk group (group 2,3). PS, family history, CDK4/6 inhibitor types were found to be related to PFS among the recurrent group.

Conclusion: There is a need for a prospective design study to determine the clinicopathological markers identifying early recurrence under CDK4/6 inhibitors so new combination therapies or alternatives can be developed.

Keywords: Breast cancer, CDK4/6 inhibitors, clinical risk factors

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Over 70% of the diagnosed breast cancer patients had hormone-positive and HER-2 negative tumors and hormonotherapy is the foremost treatment modality.[1,2] During therapy, resistance can be detected. Mostly deregulation of cyclin D-CDK4/6-pRb pathway is responsible for hormone resistance.[3] Cell cycle dysregulation leads to abnormal proliferation, which is the primary characteristic of the tumor cell.[2] In hormone-positive metastatic breast

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cancer therapy, proteins as CDK4/6 enzymes involved in the cell cycle control points are important targets for treatment.[2] Palbociclib, ribociclib, and abemeciclib are the orally active drugs that inhibit CDK4/6 that prevent the phosphorylation of RB, leading to arresting the proliferation of tumor cells.[2,4]

PALOMA 2 trial demonstrated a reduction in the risk of progression or death with the combination of letrozole and palbociclib (PFS:27.5 vs. 14.5months, HR0.58) in the first line settings of metastatic hormone-positive breast cancer.[5] In the endocrine-resistant group (PALOMA 3), median progression-free survival (PFS) was 9.5 months with palbociclib and fulvestrant combination and was 4.6 months with fulvestrant alone.[6] In MONALEESA 2 study,[7] ribociclib, was reported to have a PFS advantage with letrozole in first-line and with fulvestrant in second line settings.[8,9] The addition of abemaciclib to letrozole in metastatic 1st line settings also resulted in 50% decreased risk of recurrence[10] and increased PFS when combined with fulvestrant in the hormone-resistant group.[11]

One-fifth of the patients treated with CDK4/6 inhibitors have no response to treatment.[12] While primary resistance to CDK4/6 inhibitors can be seen in 15-30% of the patients, acquired resistance is also common during therapy.[1] In palbociclib trials, patients with prior endocrine resistance and visceral metastasis experienced shorter PFS than the non-visceral metastasis in palbociclib combined with the fulvestrant group(9.2 vs 16.6 months).[13] Subgroup analysis of all three studies could not find any potential clinicopathological characteristics that had no benefit from the addition of the CDK4/6 inhibitors to hormonotherapy.[13] Combination of CDK4/6 inhibitors with hormonotherapy was beneficial on PFS regardless of the line of therapy, CDK4/6 type, site of metastasis, or length of the treatment-free interval, age, or menopausal status.[3] Until now, no clinically available biomarkers other than estrogen/progesterone receptor (ER/PR) status have been found to be useful to predict the response.[14] There is an increasing need to define the clinical groups of patients who will obtain the most benefit. This study aimed to categorize patients concerning the clinicopathological predictive models to determine the patients with the longest PFS by adding CDK4/6 inhibitors to hormonotherapy.

Methods

This study consisted of 229 metastatic, hormone-positive, HER2 negative breast cancer patients treated with CDK4/6 inhibitors combined with standard hormonotherapy in Istanbul from 2017 to 2021. All patients who were treated with one of the CDK4/6 inhibitors in the first-line or later were included if all information could be obtained from the patients file after local Ethical Committee consents were taken (date:15 September 2021, number 2021-14/01).

Histopathological features were assessed on paraffin-embedded tissue and stained with hematoxylin and eosin. Immunohistochemical analysis of ER, PR, HER2, and ki67% levels were evaluated by an experienced pathologist in Oncology Center in Istanbul. Hormone receptor positivity was defined as a cut-off value of 1% for both ER and PR. Pathologists scored HER2 by IHC staining as 0, 1+, 2++, or 3+ based on the intensity and proportion of membrane staining.[15] IHC on the Ventana Discovery autostainer using MIB-1 antibody was used to evaluate ki 67%.

The clinicopathological factors related to PFS were analyzed, and median ER and PR expression, ki67 levels, metastatic site, metastasis number, and grade were found to be associated with recurrence among all groups and accepted as risk factors for recurrence. Patients were classified according to the presence of these poor prognostic factors as; group 1 included patients with 0-1 risk factors, group 2 with 2-3 risk factors, and group 3 with ≥4 risk factors.

Statistical Analysis

Statistical analyses were performed using SPSS 20.0(SPSS Inc., Chicago, IL, USA) software. Descriptive analysis examined the distribution of study-level variables. Survival analysis and curves were established according to the Kaplan-Meier method and compared using the log-rank test. PFS was defined as the elapsed time from the day of CDK4/6 inhibitors were added to hormonotherapy to treatment discontinuation in metastatic settings. PFS was analyzed by using the Kaplan-Meier method. Univariate analyses of prognostic factors related to survival were performed by the Cox proportional hazards model. The relationship between median PFS of 6.5 months predictive groups and other clinicopathological factors was analyzed using the Chi-square test. All p values were two-sided in tests, and p values less than or equal to 0.05 were considered significant.

Results

Totally 229 patients were included. Patients who were progressed while using CDK4/6 inhibitors were analyzed retrospectively. The clinicopathological characteristics are described in Table 1, 2. The median age was 52; nearly half were premenopausal(52%). The median ER, PR expression, and ki 67% levels were 90, 60, and 25%, respectively. 65.1% of the patients had a high level of ER expression

Table 1. The clinicopathological features of all groups

	Median	Range
Age (yr)	70	27-89
ER (%)	90	10-100
PR (%)	60	0-100
Kİ67 (%)	25	2-80
OS (mo)	48.7	3.4-388.6
PFS (mo)	9.1	1.1-48.6

ER: estrogen recptor; PR: progesteron receptor; yr: year; OS: overall survival; PFS: progression free survival; mo: month.

(>median 90), 53.7% of the patients had high-level PR expression according to median level (PR>60). Ki67 levels were over 25% (median level) in 121 patients. At the initiation time of CDK4/6 inhibitor combined with hormonotherapy, the metastasis site was visceral in 120 patients (52.4%), with 42.8% of them having multiple metastases. The most frequently used CDK4/6 inhibitors were ribociclib(73.8%), palbociclib(23.1%), and abemaciclib(3.1%) in order of frequency. Nearly half of the patients received CDK4/6 inhibitors as first-line settings (49.8%). Progression was detected in 95 (41.5%) patients after using CDK4/6 combined with hormonotherapy. The median PFS time for all groups was 18.4 months and five years of OS was 92% months during 48 months of follow-up time. Median PFS was found to be related with median ER (P=0.02), PR expression (p=0.008), histological grade(p=0.02), median ki67%(p=0.03), metastatic site(p=0.04) and metastasis number (p=0.02) prior to beginning therapy of CDK4/6 inhibitor combination. Patients with metastatic breast cancer with higher ER, PR expression lived longer without progression than patients with lower hormone levels. In addition, median ki67% and grade were inversely correlated with PFS time. Also, patients with non-visceral metastasis with lower tumor burden had longer PFS times. Because of toxicity, mostly grade 2 neutropenia and fatigue, dosage adjustment had to be performed in 89 (38.9%) patients, but that was not related with PFS. The results of the PFS levels are shown in Table 3.

The median PFS was 6.5 months in 95 patients who were progressed while being treated by CDK4/6 inhibitors. Predictive model risk groups(p=0.04), lymphovascular invasion (LVI) (p=0.03), number of metastasi (p=0.03), metastatic site before CDK4/6 inhibitors (p=0.03), and response to therapy(p<0.001) were different among patients who were categorized according to median PFS of 6.5 months.Patients with single metastasis or non-visceral metastasis had longer PFS than patients with visceral and multiple metastases. Patients who were progressed under CDK4/6 inhibitors also had shorter than 6.5 months

Table 2. The frequency table of all groups

	Number	%
PS		
0	129	56.3
1	91	39.7
2	9	3.9
Chronical disease		
Present	78	34.1
Absent	151	65.9
Family history		
Present	51	22.3
Absent	178	77.7
Menapausal status		
Premenapouse	119	52
Potmenapouse	110	48
ER %		
<90	80	34.9
≥90	149	65.1
PR		
Positive	202	88.2
Negative	27	11.8
PR %		
<60	106	46.3
≥60	123	53.7
Kİ67 %		
<25	108	47.2
≥25	121	52.8
Grade		
1	27	11.8
2	142	62
3	60	26.2
Lymphovascular invasion		
Present	68	29.7
Absent	52	22.7
Unknown	109	47.6
Perineural invasion		
Present	55	24
Absent	63	27.5
Unknown	111	48.5
Cdk4/6 inhibitor		
Ribociclib	169	73.8
Palbociclib	53	23.1
Abemeciclib	7	3.1
Cdk4/6inhibitors line		
1st line	114	49.8
2nd line	101	44.1
≥3rd line	14	6.1
Dose adjustment		
Present	89	38.9
Absent	140	61.1
Before CDK4/6 inhibitors metastasis site		
Nonviseral	109	47.6
Visseral	120	52.4
Progression after CDK/6 inhibitor		
Present	95	41.5
Absent	134	58.5

ER:estrogen recptor, PR:progesteron receptor, PS:performance score.

Table 3. The parameters related with PFS in univariate analysis

Patological characteristics	Median PFS (month)	Range	p
PS			
0	21.9	19-24.7	0.03
1	12.8	9.9-15.6	
2	7.7	0-19.7	
ER (%)			
<90	12.8	8.0-16.8	0.02
≥90	23.1	14.6-31.5	
PR (%)			
<60	12.8	10-15.7	0.008
≥60	na	na	
Histological grade			
1	na	na	0.02
2	23.1	12.6-33.5	
3	12.6	10.9-14.3	
Ki67 (%)			
<25	23.3	na	0.03
≥25	12.8	7.6-18	
Metastasis before CDK4/6			
Nonviseral	20.3	13.9-26.7	0.04
Visseral	12.8	6.9-18.6	
Number of metastasis			
Single	21.9	15.6-28.2	0.02
Multiple	11.5	7.7-15.3	
CDK4/6 line			
1st line	21.9	na	<0.001
2nd line	11.5	8.2-14.8	
3rd line	8.8	3.3-14.2	
Response to CDK4/6 inhibitors			
PR	20	3-14	<0.001
SD	19.2	2.4-14.5	
PD	4	0.5-3	
CR	na	na	

ER: estrogen recptor; PR: progesteron receptor; PFS: progression free survival; CR: complete response; PR: partial response; SD: stable disease, PD: progressive disease.

of PFS. Patients who had 0-1 risk factor clinically also progressed longer than 6.5 months compared the group 2 and group 3. The median PFS of patients with 0-1 risk factors was 8.6 months, 5.3 months with 2-3 risk factors, and 6.8 months in patients with more than 4 risk factors (p=0.03). The related factors according to median PFS of 6.5 months among recurrent patients were shown in Table 4. The metastasis site, type of CDK4/6 inhibitors, response to therapy, and the predictive model risk groups were found to be independent predictive markers for PFS in multivariate analysis (Table 5).

Discussion

Hormonotherapy for metastatic breast cancer are well tolerated and effective therapy, but during follow-up, resistance will eventually occur. CDK4/6 inhibitors combined with hormonotherapy, which overcome the endocrine resistance, have improved PFS and OS in patients with HR-positive, HER-2 negative breast cancer.[16] Which clinicopathological characteristics can affect the duration of response and early failure to these drugs remain unanswered. We developed a clinical model including significant risk factors for PFS to predict early recurrence with the treatment of CDK4/6 inhibitors. This predictive model is thought to be more objective, easily repeatable, and reliable than pathological characteristics.

Both clinical and molecular markers to identify groups most likely to benefit from CDK4/6 inhibitors are not precisely known. Patients with liver metastasis, negative PR, high-grade tumors, and short treatment-free interval(<36 months) had a poor prognosis. These high-risk patients derived the most considerable benefit from the addition of abemeciclib in the MONARCH 3 study.[16] The addition of CDK4/6 inhibitors to hormonotherapy either in first-line or later line settings improved survival regardless of menopausal status, age, histopathological types, PR status.[3,13] Gao et al. analyzed three randomized breast cancer trials of CDK4/6 inhibitors to investigate the benefit of adding CDK4/6 inhibitors in patients whose tumors might have different degrees of endocrine sensitivity.[18] They categorized patients according to a disease-free interval (< or>12 months), PR negativity, bone-only metastasis, de-novo metastasis, and age. They found that PFS was improved in all prespecified clinicopathological subgroups with the addition of CDK4/6 inhibitors.[18] Median PFS of all our groups was 18.4 months in retrospective analysis. We evaluated PFS for all patients treated with CDK4/6 inhibitors for 1st line or advanced settings, so we didn't compare with only the hormonotherapy group.

There are a lot of preclinic and clinical studies related with the mechanism of resistance to CDK4/6 inhibitors that are present without evidence of predictive values.[1] PALOMA-3 couldn't show any marker predicting the response to CDK4/6 inhibitors.[6] But patients with prior resistance to hormonotherapy and visceral metastasis experienced shorter median PFS compared to patients with non-visceral metastasis with the addition of palbociclib to fulvestrant.[6]

Cristofanilla et al. reported 29% of the patients had long term benefits over 18 months of PFS with the addition of palbociclib to fulvestrant in the endocrine-resistant group of PALOMA 3 study.[6] Nearly half of (41.5%) our patients were progressed under CDK4/6 inhibitor combination

Table 4. The differences of the clinicopatological features according to recurrence time

Clinicopatological features	PFS <6.5 month	%	PFS≥6 month	%	p
Lymphovascular invasion					
Present	11	33.3	22	66.7	0.03
Absent	15	68.1	7	31.8	
Unknown	21	52.5	19	47.5	
Number of metastasis					
Single	17	38.6	27	61.4	0.03
Multiple	30	58.8	21	41.2	
Metastasis site before CDK4/6inhibitors					
Nonvisceral	14	35.8	25	64.2	0.03
Visceral	33	58.9	23	41.1	
Response to CDK4/6 inhibitors					
PR	3	11.1	24	88.9	<0.001
SD	2	28.5	5	71.5	
PD	41	70.6	17	29.4	
CR	1	33.3			
Risk groups			2	66.7	0.04
0-1	5	31	11	69	
2-3	25	63	14	36	
≥4	17	42.5	23	57.5	

PFS: progression free survival; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table 5. The result of the multivariate analysis for PFS

Clinicopathological characteristics	Wald	p	%95 CI
PS	0.52	0.8	0.67-1.65
Family history	4.61	0.03	0.29-0.94
Metastasis site	0.36	0.5	0.88-1.25
Number of metastasis	2.61	0.1	0.87-4.19
CDK4/6 type	5.2	0.02	0.37-0.92
Response to CDK4/6 inhibitors	8.28	0.04	1.11-1.77
Risk groups	5.9	0.05	0.35-1.52

PFS: progression free survival; PS: performance score.

with a median 6.5 months of PFS. 47 of them recurred shorter than 6.5 months, which is shorter than the literature reported. This difference might originate from our study, including different lines of therapy both in first-line or endocrine-resistant groups, and other CDK4/6 inhibitor drugs were used. The presence of single, non-visceral metastasis and patients with objectively responded groups were associated with longer PFS.[6] In addition, baseline ER expression was not related to treatment duration, while PR expression impacted the long-term response rates, both fulvestrant and fulvestrant-palbociclib groups.[6] Similarly, we found median ER, PR, Ki 67, and grade were related with PFS. Some of the randomized clinical trials have confirmed the clinical relationship of ER,[17] PR expression,[16] ki 67% level[2,18,19] as predictive factors for progression.[2] Ki67 is a proliferative marker that was found to be related to the sensitivity to chemotherapy.[15] The changing level of ki67% in response to palbociclib has been used as a marker of drug sensitivity, but pre-treatment ki67 was not found to be associated with response in the PALOMA1-2 study.[15,20] Also, there was no impact of the level of ER expression or ki67 levels immunohistochemically on the predictive role of palbociclib.[15,20] Palleschi et al. also evaluated retrospectively 71 metastatic breast cancer treated with CDK4/6 inhibitors, both in the first and second line.[2] Palbociclib was the most commonly used (88.7%) drug different from our study. Ribociclib has been used commonly in our country because it is reimbursed by government insurance both in premenopausal and menopausal patients. They found that ki67 but not PR was inversely associated with PFS.[2] They used ki67 cut-off as 20% according to the St. Gallen guidelines.[21] We used median ki67 of 25% as a cut-off value to evaluate the effect of PFS. Our study showed that not only PR or ki67 also other factors, including metastatic site, metastatic number, and ER expression, can affect the recurrence time that was categorized regarding the cut-off point median 6.5 months. The main limitation is the lack of standardization in determining the cut-off levels ER, PR expression, or ki67% in predicting PFS in different clinical

studies. We used the median levels for these parameters in our groups.

Kim et al. evaluated clinical parameters to predict primary resistance of palbociclib combination with hormonotherapy in first-line settings among 305 metastatic HR-positive breast cancer patients.[19] They observed progression in 123 cases, with 12.5% having shorter than 6 months of PFS. We detected progression among 49.5% of our patients earlier than 6.5 months under CDK4/6 inhibitors combination. But we included not only first line (49.8%) but also advanced line therapy as study groups. The presence of liver metastasis, primary resistance to HT, elevated ca15.3 level, low level of expressed ER, presence of BRCA2 mutation, and higher level ki67 were associated with short PFS duration.[19] They developed a prediction model according to these characteristics and divided the patients into 4 risk groups. These four groups had different PFS with inverse relation with the presence of risk factor number and PFS time[19]. Similarly, we used predictive models including risk groups instead of using these clinicopathological parameters separately to determine the predictive importance. In our study, patients who had 0-1 risk factors clinically progressed longer than 6.5 months compared the group 2 and group 3. To the best of our knowledge, there is no known study to evaluate the relationship between clinicopathological factors in terms of HR expression, ki67% levels, and recurrence time of metastatic breast cancer under the treatment of CDK4/6 inhibitors combined with hormonotherapy. The major limitations of our study are retrospective nature and including heterogeneous groups which were consisted of patients treated with different CDK4/6 inhibitors for different lines.

Conclusion

The results of our study suggested that predictive groups which were categorized according to the presence of poor prognostic clinicopathological factors can be used to categorize patients before starting of CDK4/6 inhibitors combination. So, we can have the opportunity to predict early recurrence by using a predictive model.

Disclosures

Ethics Committee Approval: This study consisted of 229 metastatic, hormone-positive, HER2 negative breast cancer patients treated with CDK4/6 inhibitors combined with standard hormonotherapy in Istanbul from 2017 to 2021. All patients who were treated with one of the CDK4/6 inhibitors in the first-line or later were included if all information could be obtained from the patients file after local Ethical Committee consents were taken (date:15 September 2021, number 2021-14/01).

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