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Effect of Prognostic Nutritional Index and Systemic Immune-inflammation Index Changes on Progression-free Survival in Patients Treated with CDK4/6 Inhibitors and Letrozole

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ABSTRACT

Objective: CDK4/6 inhibitors are the standard of care for metastatic hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer. Markers for predicting prognosis and survival during follow-up of these patients are not yet available. Therefore, this study aimed to examine the effect of changes in prognostic nutritional index (PNI) and systemic immune-inflammation index (SII) on survival in patients treated with CDK4/6 inhibitors plus letrozole.

Material and Methods: This was a retrospective study of 88 patients. Both PNI and SII values were calculated just before, at 3 months, and at 6 months. Changes at 0-3 months and 0-6 months were divided into two groups: increasing and decreasing. Changes in progression-free survival (PFS) between these two groups were analyzed.

Results: PFS was 28.2 months [95% confidence interval (CI): 23.6-32.89] in the PNI-increasing group and 23.3 months (95% CI: 15.55-31.21) in the PNI-decreasing group at the 3rd month of treatment (p=0.048). At 6 months, PFS was 29.1 months (95% CI: 24.2-33.9) in the PNI increasing group and 23.2 months (95% CI: 15.9-30.6) in the PNI decreasing group. In the group with decreased SII at 3 months, PFS was almost 7 months longer than in the group with increased SII. At month 6, PFS was 27.7 months (95% CI: 23.4-32.1) in the SII-decreasing group and 14.8 months (95% CI: 10.5-19.1) in the SII-increasing group (p=0.017). In multivariate Cox regression analysis, only a reduction in SII between 0-6 months was a negative independent risk factor for PFS, hazard ratio 0.24 (95% CI: 0.06-0.87), p=0.031.

Conclusion: A decrease in PNI during follow-up is associated with poor survival in metastatic HR-positive and HER2 negative patients receiving letrozole in combination with a CDK4/6 inhibitor, whereas a decrease in SII may be a prognostic indicator in these patients.

Keywords: Breast cancer; CDK4/6 inhibitors; PNI; SII

INTRODUCTION

Breast cancer remains the most common cancer in the world, accounting for approximately 30% of all cancers in women, with a mortality rate of 15%.[1] Breast cancer is very heterogeneous and is clinically divided into three main subtypes based on the presence or absence of molecular markers for estrogen or progesterone receptors and human epidermal growth factor receptor 2 [Erb-B2 receptor tyrosine kinase 2 (ERBB2); formerly HER2]: hormone receptor (HR)-positive /ERBB2 negative (70% of patients), ERBB2 positive (15-20%), and triple negative (15%).[2] Therapeutic options have increased substantially in recent years for both locoregional and systemic therapy, and avoiding both overtreatment and undertreatment has become a major focus. Therapeutic approaches need to be decided in a multidisciplinary setting, taking into account molecular subtype and locoregional tumour burden. Endocrine therapy is the standard treatment

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for hormone-positive breast cancer unless the tumour burden is high. In patients with estrogen receptor-positive and HER2-negative metastatic breast cancer, a CDK4/6 inhibitor (ribociclib, palbociclib or abemaciclib) in combination with endocrine therapy should be considered standard therapy.[1] In comparison with endocrine therapy alone, this combination results in a higher response rate, a progression-free survival (PFS) benefit, and a substantial increase in overall survival (OS) while maintaining or improving quality of life. In *de novo* or recurrent metastatic breast cancer, CDK4/6 inhibitors may be combined with an aromatase inhibitor (anastrazole and letrozole; preferably in the setting of endocrine-sensitive disease) or fulvestrant (in endocrine-resistant disease), in first-line or subsequent lines.[3]

Nutrition influences the incidence, natural history, and therapeutic response of malignant diseases in both humans and preclinical animal models. Progressive weight loss is common in patients with advanced cancer, leading to a decline in performance status and quality of life. However, the management of these problems has not been generalized due to a lack of a clear understanding of the underlying mechanisms.[4,5] Nevertheless, several preclinical studies have shown that dietary interventions potentiate anticancer therapy and improve cancer outcomes. These findings are in the process of being translated into practice, with early-stage clinical data supporting their feasibility and safety.[6] Not only nutrition but also inflammatory processes play a role in cancer development.[7] The tumor microenvironment is strongly inflammatory, and small changes in inflammatory cell profiles can influence tumor development and progression, including tumor cell proliferation, invasion, migration, and metastasis. Recent clinical and epidemiological studies have also revealed that the inflammatory response is associated with breast cancer and could potentially be targeted for tumor treatment or measured as a prognostic indicator.[8,9]

The prognostic nutritional index (PNI), which was used many years ago to determine the nutritional status of patients undergoing surgery in the postoperative period, has been simplified as a calculation of serum albumin concordance and peripheral blood lymphocyte count, it is calculated as [10 × serum albumin (g/dL)] + [total lymphocyte count ($\times 10^9$/l) × 5], and in the last few years it has been examined in studies to determine whether it can also indicate prognosis in malignancies. Although there are differences between studies, low PNI has been associated with poor prognosis.[10-12] The systemic immune-inflammation index (SII) is defined as the ratio of neutrophils × platelets/lymphocytes in peripheral blood. In several studies, increasing SII values have been associated with reduced survival and poorer prognosis.[13,14]

In metastatic HR-positive and HER2-negative disease, patients without hormone resistance were selected; therefore, the study was designed to include patients receiving a combination of letrozole and CDK4/6 inhibitors. In our study, we aimed to investigate whether changes in PNI and SII at the beginning of treatment and during follow-up affect PFS in patients receiving letrozole with CDK4/6 inhibitors.

MATERIAL AND METHODS

Study Population

In this retrospective study, we evaluated patients with HR-positive HER2-negative metastatic breast cancer who were followed up at the Department of Medical Oncology of Necmettin Erbakan University Faculty of Medicine between June 2020 and June 2023 and received CDK4/6 inhibitors (ribociclib or palbociclib) and letrozole as first-line treatment. Age at diagnosis, presence of comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status, pathological subtype, tumor grade, and sites of metastasis were recorded. Patients under 18 years of age, HR-positive, HER2-positive patients, and patients receiving chemotherapy before CDK4/6 inhibitor therapy were excluded. However, patients were excluded if they met any of the following criteria: recent blood transfusions (within the last month); hematologic disorders; inflammatory or autoimmune diseases; bone marrow metastases; or use of medications that could affect the blood values related to these indices.

Variable Measurement and Definition

PNI was calculated as [10 × serum albumin (g/dl)] + [total lymphocyte count ($\times 10^9$/l) × 5] and SII as neutrophils × platelets/lymphocytes, both from peripheral blood results. PNI and SII were calculated 1 week before starting letrozole with a CDK4/6 inhibitor and at 3 and 6 months after treatment. At 3 and 6 months, two groups were defined based on changes in PNI and SII relative to pretreatment values: a group with increasing PNI and SII and a group with decreasing PNI and SII.

PFS was defined as the time to progression while receiving a CDK4/6 inhibitor or to death occurring during treatment. In patients without progression, PFS was calculated as the time to data entry.

This study approved by the Necmettin Erbakan University, Non-Drug and Non-Medical Device Research Ethics Committee (approval number: 2024/4787, date: 02.02.2024) and due to the retrospective nature of the study, the requirement for informed consent was waived.

Statistical Analysis

Clinical, pathologic, and demographic characteristics and blood sample results were obtained from the patient files and the hospital database. Since our study was characterized as retrospective and cross-sectional, no sample size calculation was required. Chi-square and Fisher's exact tests were used for descriptive statistics. For measurable evaluations, Student's t-test was performed for variables with a normal distribution, with results reported as mean and standard deviation (SD), and the Mann-Whitney U test was performed for variables with a non-normal distribution, with results reported as the median. Non-parametric tests: two or more related samples were used for dependent statistics with more than two variables. A Kaplan-Meier survival curve was used to estimate survival, and the log-rank test was used to compare survival times. All variables affecting prognosis and PFS were evaluated first by univariate and then by multivariate Cox regression analyses. The chi-squared test or Fisher's exact test was used to assess the association between categorical variables. All statistical analyses were performed using IBM SPSS Statistics 22.0 (Armonk, New York,United States, USA). Two-sided p-values <0.05 were considered statistically significant.

It was seen that the accepted limit value for PNI was taken different cut-off values by receiver operating curve analysis in the various studies. Although the generally accepted limit for SII was not clearly defined in the studies, different cut-off values were determined using receiver operating characteristic (ROC) curve analysis according to each study's design. Considering that this approach is not sufficient as a prognostic criterion for treatment follow-up, instead of determining a cut-off point, we compared changes in the patients' indices at the 3rd and 6th months with those at the beginning of treatment and categorized the changes as increasing or decreasing. Survival analyses were performed for these two groups.

RESULTS

A total of 88 patients who received letrozole with a CDK4/6 inhibitor in the first-line setting were women. Sixty-six (75%) of the patients were receiving ribociclib and twenty-two (25%) were receiving palbociclib. The mean age of all patients was 57.57 years(SD=14.1). The most common pathology was invasive ductal carcinoma (n=77; 87.5%).

Grade 2 tumors were the most common (39 patients; 44.3%), and the median value of Ki-67 was 20 (10-40). The mean body mass index (BMI) was 28.2 (SD=6.85), and 39 (44.3%) of the patients had at least one comorbidity. HER2 low status was observed in 51.1% of cases, and the two most common synchronous metastatic sites were bone (67; 76.1%) and lung (31; 35.2%). Nineteen (21.4%) patients died during follow-up (Table 1).

Tables 2 and 3 show the changes in PNI and SII, respectively. As shown in Figure 1, the median PFS was 28.2 months [95% confidence interval (CI): 23.6-32.89] in patients with a positive change in PNI at 3 months, compared with 23.3 months (95% CI: 15.55-31.21) in those with a negative change in PNI. This difference was statistically significant (p=0.048). In patients receiving ribociclib, PFS was 33.4 months (95% CI: 27.9-39) in the group with a positive PNI change and 24.7 months (95% CI: 14.9-34.5) in the group with a negative PNI change between baseline and month 3 (p=0.035). In patients receiving palbociclib, PFS was 21.1 months (95% CI: 15-27.1) in the positively changed group and 14 months (95% CI: 8.7-19.2) in the negatively changed group; however, the difference was not statistically significant because the curves crossed early.

As shown in Figure 2, PFS was 29.1 months (95% CI: 24.2-33.9) in patients with a positive change in PNI at 6 months compared with baseline, and 23.2 months (95% CI: 15.9-30.6)

TABLE 1: Demographic, clinical, and pathologic characteristics.

All patients	n=88
Age	57.57 (SD=14.1)
Age at diagnosis	54.88 (SD=15.6)
ECOG-PS- no. (%)	
0	53 (60)
1	24 (27)
2	11 (13)
At least one comorbidity- no. (%)	39 (44.3)
Pathology- no. (%)	
Invasive ductal carcinoma	77 (87.5)
Invasive lobular carcinoma	9 (10.2)
Mixed type (IDC + ILC)	2 (2.3)
Tumor grade- no. (%)	
1	13 (14.8)
2	51 (57.9)
3	24 (27.3)
Metastasis site- no. (%)	
Bone	67 (76.1)
Lung	31 (35.2)
Brain	10 (11.3)
Liver	20 (22.7)
Adrenal gland	4 (4.6)
Death- no. (%)	19 (21.4)

SD: Standard deviation; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; ECOG-PS: Eastern Cooperative Oncology Group performance score.

TABLE 2: Prognostic nutritional index (PNI).	
	All patients, n=88
Pre-treatment PNI, median (IQR)	52.2 (46.6-56.3)
3rd month PNI, median (IQR)	52 (48-55.7)
6th month PNI, median (IQR)	51.9 (49.1-55.4)
p-value, median (IQR)	**0.031**
When all patients were considered, the PNI value decreased at 3 and 6 months after the start of treatment; this decrease was statistically significant (p=0.031). IQR: Interquartile range.	

TABLE 3: Systemic immune-inflammatory index (SII).	
	All patients, n=88
Pre-treatment SII, median (IQR)	595.3 (352.1-1171.1)
3rd month SII, median (IQR)	261 (166.5-496.9)
6th month SII, median (IQR)	272.6 (161.5-468.3)
p-value, median (IQR)	**<0.001**
When all patients were evaluated, a significant decrease in SII was observed after the start of treatment and this was statistically significant (p=0<0.001). IQR: Interquartile range.	

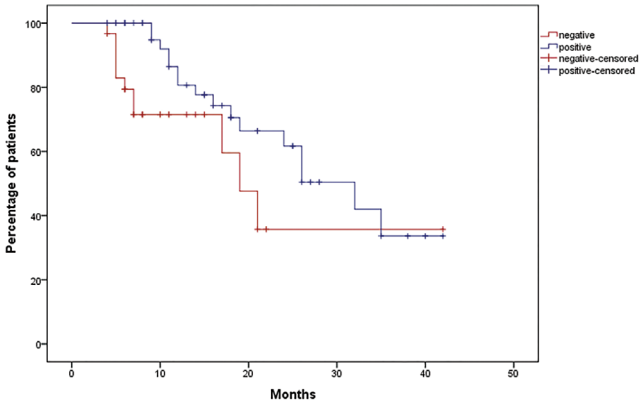

FIGURE 1: PFS in patients with positive or negative change of PNI at 3 months compared to baseline.

PNI: Prognostic nutritional index; PFS: Progression-free survival

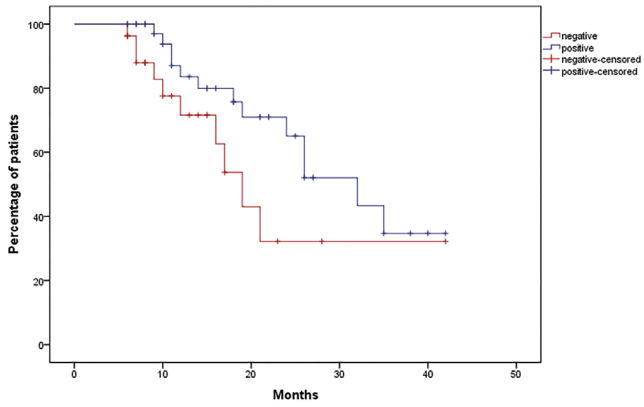

FIGURE 2: PFS in patients with positive or negative change of PNI at 6 months compared to baseline.

PNI: Prognostic nutritional index; PFS: Progression-free survival

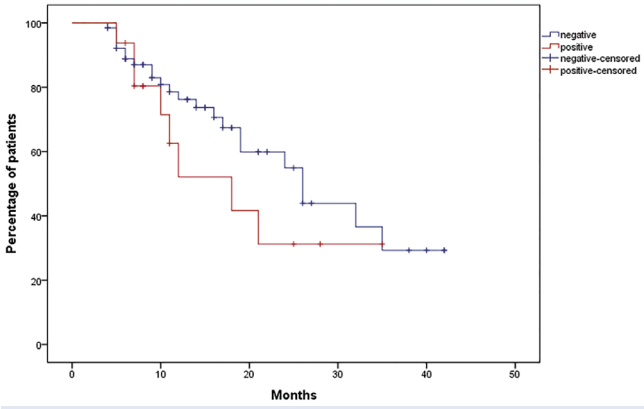

FIGURE 3: PFS in patients with positive or negative change of SII at 3 months compared to baseline.

SII: Systemic immune-inflammation index; PFS: Progression-free survival

in patients with a negative change; p=0.091, which was not statistically significant. In patients receiving ribociclib, PFS was 33.5 (95% CI: 27.5-39.5) months in the group with a positive change in PNI at 6 months and 28.7 (95% CI: 19.7-37.7) months in the group with a negative change; the p value was not statistically significant. In patients receiving palbociclib, PFS was 22.8 (95% CI: 16.1-29.5) months in the group with a positive change in PNI at 6 months, whereas it was 12.4 (95% CI: 7.7-17.2) months in those with a negative change; the difference was statistically significant (p=0.031).

As shown in Figure 3, for all patients, PFS was 25.8 (95% CI: 21.4-30.3) months in those with decreasing SII at 3 months compared to baseline, while PFS was 19.3 (95% CI: 12.7-26) months in those with increasing SII. Although PFS was numerically better in patients with decreasing SII, the difference was not statistically significant (p=0.306). Figure 3 shows that the curves crossed each other early. Among patients receiving palbociclib, PFS was 21.7 (95% CI:15.6-27.9) months for those with decreasing SII at 3 months and 10.7 (95% CI: 5.6- 15.8) months for those with increasing SII (p=0.023). In patients receiving ribociclib, PFS was 23.4 (95% CI: 15-31.7) in patients with increasing SII and 28.6 (95% CI: 22.9-34.3) in patients with decreasing SII at 3 months; the difference was not statistically significant.

As shown in Figure 4, among all patients, PFS was 14.8 months (95% CI: 10.5-19.1) in patients with increased SII at 6 months, compared with 27.7 months (95% CI: 23.4-32.1) in patients with decreased SII; the difference was statistically significant (p=0.017). In patients receiving palbociclib, at month 6, PFS was 9 months (95% CI: 5-12.9) in those with increasing SII and 20.8 months (95% CI: 15-26.5) in those with decreasing SII (p=0.028). This was not statistically significant for ribociclib,

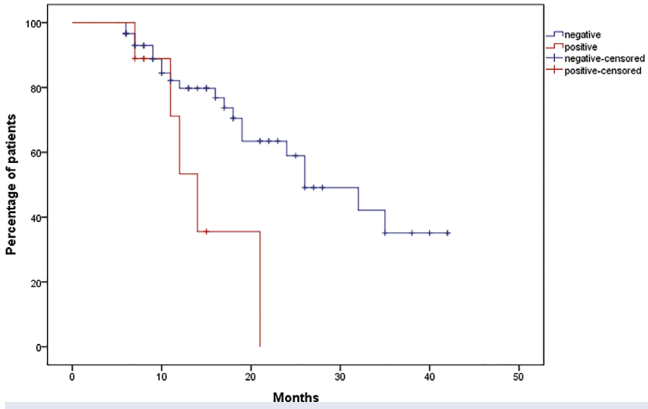

FIGURE 4: PFS in patients with positive or negative change of SII at 6 months compared to baseline.

SII: Systemic immune-inflammation index; PFS: Progression-free survival

although numerically PFS was higher in patients with decreasing SII [32.3 months (95% CI: 27-27.5) vs. 17 months (95% CI: 12.1-21.8); p=0.065].

Factors affecting prognosis were evaluated first by univariate and then by multivariate Cox regression analyses. A model was created including the following variables: age at diagnosis; ECOG 0 performance status; presence of comorbidity; presence of invasive ductal carcinoma; presence of bone, lung, and liver metastases; PNI 0-3 months difference; PNI 0-6 months difference; SII 0-3 months difference; and SII 0-6 months difference. Only a decrease in SII between 0-6 months was an independent risk factor for PFS, with a hazard ratio of 0.24 (95% CI: 0.06-0.87; p=0.031). Correlation was analyzed for the change in SII from 0 to 6 months, which was the only independent variable in terms of PFS. The correlations were 0.385 (p<0.001) for SII 0-3 months change, -0.082 (p=0.404) for PNI 0-3 months change, and -0.095 (p=0.323) for PNI 0-6 months change.

DISCUSSION

In this study, patients with HR-positive and HER2-negative metastatic breast cancer who received letrozole in combination with a CDK4/6 inhibitor had better PFS and showed increased PNI and decreased SII during follow-up. This is the first study in the literature to examine both SII and PNI at specific time points and to evaluate their effects on PFS in this patient group.

According to the World Cancer Research Fund/American Institute for Cancer Research recommendations, maintaining a healthy body weight, being physically active, eating a diet high in fiber and limiting fat intake (saturated fatty acids if possible) can improve OS after a breast cancer diagnosis.[15] In studies, both low BMI and the amount of weight loss independently predicted poorer OS. There is a large body of evidence supporting the clinical relevance of nutritional intervention in patients with cancer, which aims to ensure adequate energy and nutrient intake during anticancer treatment, which can lead to improved response to treatment and reduce the side effects of these therapies.[16] Malnutrition decreases survival and worsens tumor prognosis; albumin levels are known to decrease in malnutrition. Low albumin levels in cancer patients are not only associated with malnutrition but also with inhibition of albumin synthesis due to cancer-related systemic inflammation and increased albumin turnover by tumors.[17] Lymphopenia also affects prognosis in patients with metastatic cancer. The reasons for this include destruction of lymphocytes stimulated by tumor cells with proapoptotic ligands, alteration in T-cell receptor (TCR) expression and consequent decrease in the capacity of lymphocytes to respond to TCR stimulation, increase in Tregs (regulatory T-cells) that play a suppressive role in the immune system and activation-induced cell death.[18] Neutrophils in the tumor microenvironment, which are involved in systemic inflammation, have also been shown to increase tumor cell proliferation, stimulate angiogenesis, contribute to deoxyribonucleic acid damage, and be associated with metastasis.[19] Several mechanisms have been proposed to explain the relationship between high platelet counts and cancer, including the recruitment of cancer cells by platelets, increased extravasation or permeability of the basement membrane, and protection of cancer cells from the immune response in the bloodstream.[20] Considering all these biological processes, it is clear why changes in both PNI and SII can predict the behavior of tumor cells and response to therapy.

The effects of inflammation on carcinogenesis may be due to continuous and uncontrolled stimulation of the cell cycle, resulting in increased stem cell divisions and local mutagenic effects. Mutagenesis may occur as a by-product of the inflammatory agent itself, as a by-product of increased metabolism, or as a result of increased production of reactive oxygen radicals produced by cells involved in the inflammatory response.[5] In particular, monitoring the primary immune response and alterations in systemic immune status can influence both response to treatment and prognosis in patients with breast cancer.[21] One of the best and simplest indicators of this is the SII, which is derived solely from blood test results. It has been studied many times before to see if it can predict prognosis in chronic non-malignant diseases.[22,23] Recently, it has also been examined in solid tumors for which surgery is a treatment option. In breast cancer, limited studies have been conducted in the literature and high SII has been an indicator of poor prognosis in these studies.[24,25] In these studies, different SII cut-off points were used. Accordingly, patients were divided into two groups and were evaluated.

We found it appropriate to evaluate SII by grouping subjects according to whether SII increased or decreased from the start of treatment to follow-up, as was done for PNI.

PNI has long been used in patients undergoing gastrointestinal surgery because of its predictive and prognostic significance in cancer patients. It has been reported that surgery can be performed in patients with normal or low normal PNI values, and surgery should be avoided in very low patients because it will not contribute to life.[11] In the early 2000s, it was again used as a prognostic marker during the perioperative period for colon and esophageal cancers.[26,27] In the last few years, several studies have shown that PNI in breast cancer predicts prognosis. With the advantages of being convenient, non-invasive and reproducible, PNI pretreatment results were reported to be a useful prognostic indicator for locally advanced breast cancer patients receiving neoadjuvant chemotherapy and before surgery, and a promising biomarker for breast cancer in treatment strategy decisions.[28,29]

In a previous study that demonstrated that PNI serves as a prognostic marker for the use of CDK4/6 inhibitors in HR-positive and HER2-negative breast cancer and that showed a survival benefit in the high PNI group, a cut-of value of 50.4 for PNI was adopted.[30] Most studies used different values in ROC curve analysis depending on the study design. In our study, instead of using this, we grouped the patients according to whether PNI increased or decreased during follow-up. Our aim was, first, to eliminate the false cut-off value that may be population-related and therefore not generalizable, and second, to reduce the possibility that patients with PNI below the cut-off point at baseline would remain below the cut-off point even if their values increased during follow-up. For all these reasons, this study is the first to examine changes in indices at 0-6 months and the correlation between PNI and SII in patients using CDK4/6 inhibitors. We aimed to determine whether the change at 3 months was persistent and whether the negative correlation between PNI and SII persisted. Another key difference is that all patients had newly diagnosed metastases and received CDK4/6 therapy at the primary care level. Chemotherapy or radiation therapy should not have affected blood parameters as measured by both PNI and SII. Studies showing that a decrease in PNI reduces survival have included patients from all treatment lines.[31]

In a recent study in patients with acute respiratory distress syndrome, ribociclib was shown to reduce neutrophilic inflammation with its PDE4 inhibitor effect and may be offered as a new treatment option in this group of patients.[32] In another study, palbociclib was given to lupus-prone mice, and the inflammatory response was examined, and it was shown that disease-related inflammatory effects were reduced with palbociclib, albeit differently in both genders.[33] Palbociclibin, by suppressing immunoglobin E-mediated mast cell activation both *in vitro* and *in vivo*, which it does through inhibition of mast cell degranulation, has been considered for development as a treatment for mast cell-mediated allergic diseases.[34] The anti-inflammatory activity of CDK4/6 inhibitors was also observed in our study, with a significant decrease in SII in the third and sixth months of treatment. Despite CDK4/6 inhibitor treatment, PFS is significantly lower in patients with increased SII during follow-up. A rapid increase in SII during the third month may necessitate earlier radiological evaluation or closer clinical monitoring before symptomatic progression occurs; therefore, caution is warranted.

Study Limitations

Our study has several limitations, including its retrospective design, the lack of a definitive cut-off value for SII and PNI, and the short median follow-up time for both PFS and OS; therefore, the results should be interpreted in light of these limitations. The relatively small number of patients was also a limitation. The p-values for changes in both PNI and SII in CDK4/6 inhibitor users (as a whole) and in patients treated with ribociclib and palbociclib are given separately. Our aim here was to demonstrate numerically that the trends among treatments were similar, even though we acknowledged that the sample was small. The results should be confirmed in larger sample sizes. Prospective studies with larger patient cohorts are needed in which these indices are calculated at regular intervals and the impact of changes on PFS is analyzed over the long term. However, this is the first study to analyze the combination of a CDK4/6 inhibitor and letrozole as first-line treatment and to calculate index changes at 3 and 6 months.

CONCLUSION

PNI is also important, as it indicates poor survival in patients with declining PNI during follow-up. SII, which does not require pathologic or genetic examination and is measured using routine blood parameters during follow-up may be a inexpensive and easily accessible prognostic indicator in metastatic hormone-positive and HER2-negative patients receiving first-line treatment with letrozole and a CDK4/6 inhibitor.

Ethics

Ethics Committee Approval: This study approved by the Necmettin Erbakan University, Non-Drug and Non-Medical Device Research Ethics Committee (approval number: 2024/4787, date: 02.02.2024).

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Concept: A.O., Me.A., Design: A.O., Me.A., Data Collection or Processing: A.O., B.K., M.K.E., M.A., Me.A., Analysis or Interpretation: A.O., Me.A., Literature Search: A.O., Me.A., Writing: A.O., B.K., M.K.E., M.A., Me.A.

Conflict of Interest: Murat Araz Prof. MD is Associate Editor in Journal of Oncological Sciences. They had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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