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Enzalutamid Kullanan Kastrasyona Dirençli Prostat Kanserli Hastalarda Tedavi Öncesi Türetilmiş Nötrofil Lenfosit Oranı (dNLR) ile Prognoz Öngörülebilir mi?

Can the Prognosis be Predicted by the Pretreatment Derived Neutrophil to Lymphocyte Ratio (dNLR) in Patients with Castration-Resistant Prostate Cancer Receiving Enzalutamide?

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ÖZ

Giriş: Bu çalışmada, enzalutamid ile tedavi edilen metastatik kastrasyona dirençli prostat kanseri hastalarında nötrofil lenfosit oranı (NLO), derive nötrofil lenfosit oranı (dNLO), trombosit lenfosit oranı (TLO), sistemik immün-inflamasyon indeks (Sİİ) ve hemogram parametrelerinin prognostik ve prediktif önemi incelenmiştir.

Yöntem: Kocaeli Üniversitesi Hastanesi'nde (2018-2023) metastatik kastrasyona dirençli prostat kanseri tanısı konmuş 82 hastanın geriye dönük verileri incelendi. Prostat spesifik antijen, hemoglobin, nötrofil, lenfosit değerleri kaydedildi. Formüller: Sİİ = Nötrofil x Trombosit/Lenfosit; TLO = Trombosit/Lenfosit; dNLO = Nötrofil / (WBC- Nötrofil). Sağkalım, Kaplan-Meier yöntemi, Log-rank testi ve Cox regresyonu kullanılarak analiz edildi.

Bulgular: Yüksek dNLO, hastalık progresyonunda artış riski ile ilişkilendirildi (HR 2,39, CI 1,03-5,49; P=0,04), buna karşın TLO, Sİİ ve diğer hemogram değerleri ile progresyon arasında ilişki bulunmadı. Ortalama sağkalım 53,0 ± 3,8 ay bulundu. Enzalutamid tedavisi öncesi dosetaksel ile tedavi edilen ve edilmeyen hasta grupları incelendiğinde, NLO, dNLO, TLO, Sİİ ve hemogram parametreleri ile progresyonsuz sağkalım arasında bir korelasyon gösterilemedi.

Sonuç: Enzalutamid tedavisi gören hastalarda yüksek dNLO, progresyon riskinde artış ile ilişkilidir. Tedavi stratejileri belirlenirken dNLO değeri göz önünde bulundurulmalıdır.

Anahtar Kelimeler: kastrasyona dirençli prostat kanseri, enzalutamid, nötrofil lenfosit oranı

ABSTRACT

Objective: This study assessed the prognostic and predictive value of neutrophil-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and complete blood count (CBC) parameters in metastatic castration-resistant prostate cancer patients treated with enzalutamide.

Method: A retrospective review of 82 metastatic castration-resistant prostate cancer patients at Kocaeli University Hospital (2018-2023) was conducted. Parameters included prostate-specific antigen, hemoglobin, and cell counts. Formulas: SII = Neutrophil x Platelet/Lymphocyte; PLR = Platelet/Lymphocyte; dNLR = Neutrophil / (WBC - Neutrophil). Survival was analyzed using the Kaplan-Meier method, Log-rank test, and Cox regression.

Results: High dNLR was associated with increased progression risk (HR 2.39, CI 1.03-5.49; P=0.04), whereas PLR, SII, and other CBC metrics were not. The mean survival was 53.0 ± 3.8 months. Patient cohorts categorized by prior docetaxel treatment, showed no correlation between the aforementioned values and progression-free survival.

Conclusion: Elevated dNLR levels in patients undergoing enzalutamide therapy correlate with adverse outcomes, emphasizing the role of dNLR in treatment strategies.

Keywords: castration-resistant prostate cancer, enzalutamide, neutrophil to lymphocyte ratio

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INTRODUCTION

Prostate cancer (PC), one of the most prevalent malignancies among men worldwide, has seen an increase in metastatic diagnoses in recent decades.1,2 For treating PC, targeting androgen receptor signaling to block the signals is considered among the initial treatment choices. Castration-resistant prostate cancer (CRPC) represents a progressed stage of PC, marked by disease advancement despite surgical or medical (androgen deprivation) castration.3 The TAX-327 research demonstrated an improvement in overall survival (OS) for metastatic castration-resistant prostate cancer (mCRPC) patients treated with docetaxel.4 After this study, docetaxel became the standard treatment in mCRPC. Enzalutamide(ENZ), a targeted androgen receptor inhibitor, is designed to competitively bind to the ligand-binding domain of the androgen receptor. Thus, it hinders the translocation of the androgen receptor to the cell nucleus, the recruitment of cofactors to the androgen receptor, and the binding of the androgen receptor to DNA.5 The findings from the PREVAIL and AFFIRM trials indicated that for patients with mCRPC, the use of the androgen receptor (AR)-targeting agent enzalutamide led to a decrease in the risk of death.6,7 Nevertheless, there is no consensus on the order of treatment among the many therapeutic alternatives.

The systemic inflammatory response significantly influences cancer progression and plays a pivotal role. Numerous researchers have shown that parameters associated with inflammation, such as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII), could serve as prognostic indicators for patients with CRPC undergoing treatment with docetaxel chemotherapy and androgen receptor-targeting agents.8–10 However, the applicability of these indicators to patients receiving enzalutamide, a prominent androgen receptor inhibitor, remains largely unexplored. Therefore, the focus of this study was to investigate whether these inflammation-related parameters, specifically NLR, PLR, and SII, can also serve as prognostic markers for mCRPC patients receiving enzalutamide. This research aims to fill this knowledge gap and potentially provide clinicians with additional tools to predict treatment outcomes and refine therapeutic strategies.

Given the above considerations, the main question that this research seeks to answer is, 'Can NLR, PLR, and SII serve as reliable prognostic markers in mCRPC patients receiving enzalutamide, and does their prognostic value change before and after the use of enzalutamide in a docetaxel chemotherapy setting?' By resolving this question, we hope to contribute to ongoing efforts to improve prognosis and personalize therapeutic strategies for patients with mCRPC.

MATERIALS AND METHODS

Study design and patient selection:

This study was a retrospective examination of patients diagnosed with metastatic castration-resistant prostate cancer at Kocaeli University Hospital, Department of Medical Oncology between January 2018 and March 2023. A total of 138 patients were initially identified, but complete data were only available for 82 of these individuals, who consequently constituted the study cohort.

Patients with rising prostate-specific antigen (PSA) levels or imaging evidence of disease progression, even after receiving androgen deprivation therapy, were classified as having CRPC. Patients who had received only enzalutamide as a treatment and had continued surgical or medical castration using luteinizing hormone-releasing hormone (LH-RH) agonists were included in the study. Patients who received abiraterone or those without metastasis were excluded.

Data collection and parameters:

The clinical and pathological attributes of each individual were documented. These included age, serum PSA level, biopsy Gleason score, bone metastasis, visceral metastasis, progression dates, Eastern Cooperative Oncology Group (ECOG) performance status, radiological response to therapy, and blood cell counts.

Before initiating enzalutamide therapy, baseline PSA levels were recorded, and subsequent measurements were taken roughly every 6-8 weeks. Patients underwent imaging evaluations, using chest and abdominal computed tomography scans and bone scans, either at 3-6 months intervals or when exhibiting signs suggestive of disease advancement. Criteria from the Response Evaluation Criteria in Solid Tumors (RECIST) were applied to determine radiological progression in visceral and nodal metastases, whereas the identification of two or more novel bone lesions as per the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria indicated progression in bone.11

The principal objective of this research was to assess the influence of parameters such as the derived neutrophil-to-lymphocyte ratio (dNLR), SII, PLR, and other hematological metrics on progression-free survival (PFS). Overall survival (OS) was defined as the duration from the initiation of enzalutamide therapy to death from any underlying reason.

Calculation of the Indices:

The platelet-to-lymphocyte ratio was determined as: PLR = platelet/lymphocyte, and the derived neutrophil-to-lymphocyte ratio was calculated as: dNLR = Neutrophil / (WBC - Neutrophil). The systemic immune-inflammation index was computed using the following formula: SII = neutrophil x platelet/lymphocyte. Complete blood cell counts (CBCs) were acquired either on the day or shortly before starting enzalutamide therapy.

Statistical analyses

Statistical evaluations were conducted using SPSS 20.0 (SPSS, Chicago, IL, USA) and MedCalc 14 (MedCalc Software, Ostend, Belgium). To test for normality, both the Kolmogorov-Smirnov and Shapiro-Wilk tests were employed. Continuous variables are concerned, they were expressed as either mean±standard deviation or, for those not following a normal distribution, as median along with interquartile range (IQR). Categorical data are detailed as frequency (and their respective percentages). For the comparison of continuous variables across groups, we used the independent samples t-test or the Mann-Whitney U test, based on their suitability. The relationship between the two categorical datasets was explored through the chi-square test. Survival patterns were analyzed using the Kaplan-Meier method coupled with the Log-rank test, and the Cox regression approach. A p-value less than 0.05 was deemed to have statistically significant.

RESULTS

Patients characteristics:

The mean age at diagnosis for the patients was 66.15 ± 9.4 years. The median PSA value was 9.21 ng/mL (IQR:4.07 – 36.13) before enzalutamide treatment. The majority of patients exhibited metastases to the bone (n=66, 80.5%). In contrast, 13 patients displayed metastases to visceral sites (15.9%). Forty-six patients (56.1%) had an ECOG performance status of 0, 21 (25.6%) patients had a status of 1, and 15 (18.3%) patients had a status of 2. While 46 (56.1%) patients used docetaxel chemotherapy before enzalutamide treatment, 36 (43.9%) patients used enzalutamide as the first-line treatment in the metastatic stage. Twenty (24.4%) patients had a Gleason score of less than 7, and 62 (75.6%) patients had a score of 8- 10. Patient backgrounds and CBC data are displayed in Tables 1 and 2.

Table 1. Characteristics of Enzalutamide-Treated Patients

Patient Characteristics	Value
All	82
Diagnosis Age (mean ± SD)	66.15 ± 9.4 years
PSA level at diagnosis	70 ng/mL (5.85 - 5071.48 ng/mL)
ECOG performance status before treatment	
- ECOG 0	%35.4 (n=29)
- ECOG 1	%40.2 (n=33)
- ECOG 2	%24.4 (n=20)
Gleason Score	
- Score ≤ 7	24.4% (n=20)
- Score > 7	75.6% (n=62)
Bone Metastasis	
- None	19.5% (n=16)
- Present	80.5% (n=66)
Visceral Metastasis	
- None	84.1% (n=69)
- Present	15.9% (n=13)
Metastatic Tumor Volume	
- Low	64.6% (n=53)
- High	35.4% (n=29)
Prior Docetaxel	
- None	43.9% (n=36)
- Present	56.1% (n=46)

Table 2. Complete Blood Count Data

Parameters	Median(IQR)
Hemoglobin	12.69 g/dL
WBC ,x10^9/L	6.88 (5.61 - 8.66)
Neutrophil , x10^3/uL	4.12 x10^3/uL (3.30 - 5.12)
Lymphocyte, x10^3/uL	1.67 x10^3/uL (1.30 - 2.43)
Platelet, x10^3/uL	241.5 x10^3/uL (200 - 280.75)
NLR	2.47 (1.68 - 3.75)
PLR	142.39 (101.02 - 204.50)
SII	616.62 (407.17 - 911.00)

IQR: İnterquartile Range, NLR: Neutrophil–Lymphocyte Ratio, SII: Systemic İmmune-İnflammation İndex, WBC: White Blood Cell, PLR: Platelet–Lymphocyte Ratio.

The median follow-up time was 48 months (range 28-85 months). It was determined that 26 (31.7%) patients had progression at the last control date and 8 (9.8%) died.

Prognostic Factors in mCRPC Patients Receiving Treatment with Enzalutamide:

We evaluated the prognostic relevance of PLR, dNLR, SII, and CBC metrics in relation to PFS. A high dNLR [(< Median vs. ≥ Median); hazard ratio (HR), 2.39; confidence interval (CI), 1.03-5.49; P=0.04] was significantly associated with a high risk of progression (Table 3, Fig. 1). Conversely, there was no association between CBC parameters, SII, and PLR and the risk of progression (Table 3).

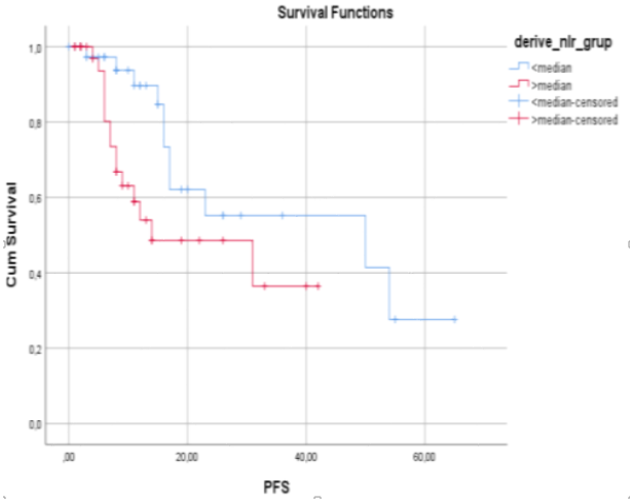

Figure 1. PFS in dNLR

Table 3. Association Between PLR, Dnlr, SII, and CBC Parameters and Prognosis in Patients Treated with Enzalutamide

Parameter	Subgroup	PFS (months)	Standard Deviation (months)	P value
Hemoglobin (HGB)	< Median	29.9	4.02	-
	≥ Median	36.5	6.09	0.56
Platelet-to lymphocyte-ratio (PLR)	< Median	35.9	5.8	-
	≥ Median	25.3	3.06	0.35
Derived neutrophil-to-lymphocyte ratio (dNLR)	< Median	39.1	5.31	-
	≥ Median	23.3	3.29	0.032
Systemic immune-inflammation index (SII)	< Median	34.9	5.15	-
	≥ Median	26.5	3.39	0.38

Progression-free survival and OS were analyzed using the Kaplan-Meier method. The mean duration of PFS was 33.9 ±4.0 months. Additionally, the PFS rate was 72.1 % at the end of the first year and 50.7% at the end of the second year. The estimated mean survival time was 53.0 ± 3.8 months. The overall survival rate was 96% in the first year, 80% at the end of the second year.

In patients diagnosed with metastatic prostate cancer who received docetaxel as the first-line treatment and enzalutamide as the second-line treatment, the PFS was found to be 33.8 ± 4.4 months. Conversely, in patients who received enzalutamide as an initial treatment, the PFS was 28.3 ± 7.0 months (P=0.92).

In the following stage, patient cohorts were established based on whether they had received docetaxel as their initial treatment or not. The effect of these groups' dNLR, SII, hemoglobin, and PLR values on PFS was analyzed. However, no significant correlation was detected between these values and PFS in these groups.

Patients with visceral metastasis had a PFS duration of 23.5± 4.7 months and those without visceral metastasis had a PFS duration of 34.6 ±4.3 months (P=0.92).

Patients whose initial PSA levels before starting enzalutamide treatment were below the median experienced a PFS duration of 37.9±5.4 months. Conversely, patients with initial PSA levels above the median had a PFS duration of 27.9±5.2 months; the difference in PFS between these two groups was not statistically significant, (P=0.26).

Upon evaluating the PSA response rate, it was observed that there was a reduction of 50% in the PSA level in 20.7% of patients (n=17), whereas a decline of more than 50% was observed in 67.1% of patients (n=55). Furthermore, an increase (progression) in the PSA level was detected in 12.2% of patients (n=10).

DISCUSSION

In recent years, researchers have focused on identifying novel biomarkers that can provide more accurate prognostic information for prostate cancer patients. One such biomarker that has gained attention is the neutrophil-to-lymphocyte ratio and its derived counterpart, the derived NLR. The current study found that an elevated dNLR level was associated with an unfavorable prognosis among patients with CRPC who underwent ENZ treatment. NLR was also identified as a predictive factor in different types of cancers.12 The association between of NLR and prognosis has been observed across various treatment approaches in cases of metastatic prostate cancer.13,14 Our research findings also mirrored those observed in routine clinical settings. In a meta-analysis by Guan et al., elevated NLR ratios were correlated with unfavorable overall survival outcomes, whereas no significant correlation was identified between NLR and PFS.13 In contrast, our study revealed a significant correlation between increased NLR and PFS, whereas no significant correlation was observed with OS.

In this study, we evaluated the potential role of PLR, SII, and CBC parameters on the prognosis of patients. However, our findings indicated that these parameters, namely PLR, SII, and CBC, were not significantly correlated with the risk of disease progression. In a meta-analysis conducted by Zhang et al., they found a significant association between high SII levels and poor OS and PFS.14 In a different research conducted by Li et al., they explored the prognostic value of PLR in urological malignancies. Their findings that a high PLR was adversely associated with OS in these cancers, except bladder cancer.15 Interestingly, Guan and colleagues' meta-analysis did not identify a significant relationship between PLR and PFS, but they did find a correlation with NLR.13 In the study conducted by Passardi et al., the effectiveness of adding bevacizumab to the treatment of patients with metastatic colorectal cancer was evaluated in relation to inflammatory parameters. It was found that in the group receiving bevacizumab, a high NLR was associated with a poorer prognosis. However, this association was not deemed significant for the SII and PLR.16 Another study investigated the relationship between pre-treatment SII and dNLR and prognosis in EGFR-mutant advanced non-small cell lung cancer patients treated with Erlotinib. In this study, shorter PFS and OS were found in groups with high SII and dNLR.17 These results collectively demonstrate the complexity of prognostic biomarkers in cancer studies and the necessity of conducting more comprehensive research in this field.For the treatment of advanced prostate cancer, new standards of care have recently been developed.

However, few randomized trials have examined which of these sequencing approaches would be the most effective for maximizing benefit and extending patient survival.18,19 While there is a need for tumor markers to foresee the effectiveness of enzalutamide sequencing, our data suggest that there was no notable link between PFS and metrics such as dNLR, SII, hemoglobin, and PLR when enzalutamide was used both before and after docetaxel treatment.

There are several constraints to our research. Because this was a retrospective study, some information about the clinical course was unavailable. The general population of patients with prostate cancer is quite heterogeneous. Advances in imaging techniques and the regular conduct of cancer-specific screening assist in the early diagnosis of the disease. Considering recent developments, patients who are closely monitored after early diagnosis are also receiving treatment in the castration-sensitive stage. For treating metastatic disease in the castration-sensitive stage, the overall survival benefit of treatments such as docetaxel, abiraterone, and enzalutamide has been demonstrated in this day.20 In our country, too, treatments such as enzalutamide, abiraterone, and docetaxel have been introduced in recent years for the treatment of metastatic castration-sensitive prostate cancer, and the number of patients who can access treatment at this stage has increased. Thus, when the ailment transitions to the castration-resistant phase, heterogeneity arises because of the treatments received in the sensitive stage. Furthermore, the sample size was relatively small. To establish the value of dNLR as a biomarker, an extended-duration investigation encompassing a broader population and a prospective study should be conducted.

In conclusion, our analysis indicates that a high dNLR correlates with unfavorable results when using enzalutamide. This underscores the potential importance of NLR as a predictive marker when considering treatment strategies with enzalutamide.

Ethics Committee Approval: This study adhered to the principles set out in the Declaration of Helsinki and received approval from the ethical review board of Kocaeli University (Approval Number: KÜ GOKAEK-2023/16.01 Proje No: 2023/173).

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