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Research Article

Prognostic Markers in the Treatment of Abiraterone Acetate + Prednisolone and Enzalutamide in Castration-Resistant Metastatic Prostate Cancer; Prognostic Value of Neutrophil Lymphocyte Ratio in Post - Docetaxel Setting

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Abstract

Objectives: To evaluate the relationship between the neutrophil lymphocyte ratio (NLR) and progression-free survival (PFS) at the start of enzalutamide or abiraterone acetate treatment in metastatic castration-resistant prostate cancer (mCRPC) at post-docetaxel setting.

Methods: Patients whom progressed after at least 6 cycles of docetaxel chemotherapy, included. Cases with <4 bone metastases, isolated lymph node metastases, or visceral metastases and uncontrolled comorbidity were excluded. Mean NLR was used for cut-off threshold.

Results: 54 cases with a median age of 69 (54-75) years, with NLR below 3.34 were determined as the low NLR group, and above determined as the high NLR group. The mean PFS of the high NLR group (n=31,57.4%) was 5.3 months and low NLR group (n=23,42.6%) was 7.2 months (p<0.001). A strong negative correlation was found between NLR level and PFS (r:0.833, p<0.001). Patients with NLR regression (n=36,66.7%, regression at 6'th week of the therapy) represents 7.0 months PFS that is higher than others (5.2 months,p<0.001). Extremity bone metastases was related with low PFS (5.1 month vs 7.1, p<0.001) and high NLR (4.55 vs 2.74, p<0.001).

Conclusion: NLR level above 3.34 and failure to achieve NLR regression in the first six weeks of treatment are poor prognostic factors.

Keywords: Abiraterone asetate, enzalutamide, prostate cancer, neutrophil lymphocyte ratio

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In the last decade, a prognostic threshold has been exceeded in metastatic castration-resistant prostate cancer (mCRPC) with chemotherapy and new generation androgen pathway inhibitors. The ideal treatment sequence is still controversial in this group of patients who live longer and have a higher quality of life expectancy. Since the

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majority of the target age group consists of patients over 65 years of age, factors such as treatment tolerability, life expectancy and quality of life are at least as important as treatment effectiveness.[1] It is clear that the efficacy of the sequential treatment of abiraterone acetate and enzalutamide after progression is weak. Because similar resistance mechanisms develop against these two agents that use the same pathway.[2]

Many studies have shown that inflammation is both a cause and a result in the pathogenesis of cancer. As the specific tumor characteristics of the patients are understood, the optimal treatment choice is shaped. The main prognostic markers are stage, PSA level and Gleason score. However, the importance of laboratory results showing tumor-supporting inflammatory activity has been demonstrated in many cancer types. In addition, inflammation may affect the immune response to the tumor and the efficacy of treatment, which may be associated with it.[3,4]

The neutrophil-to-lymphocyte ratio (NLR) is a biomarker obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. NLR has become an easy and inexpensive laboratory instrument that can be used to detect the course of systemic diseases in daily life. It has shown prognostic value in many diseases from infection to cancer. Its prognostic value in solid tumors has been repeatedly proven. There are studies showing the prognostic value of tumor-associated inflammation in prostate cancer. The prognostic value of NLR has also been proven in mCRPC.[5-8]

In our study, we aimed to evaluate the relationship between the NLR parameter and progression-free survival (PFS) at the start of enzalutamide or abiraterone acetate treatment in patients with castration-resistant prostate cancer that progressed after docetaxel treatment.

Methods

Our study included 83 patients who were followed up in Gazi Yaşargil Training and Research Hospital between January 2016 and August 2021, who received docetaxel chemotherapy with the diagnosis of mCRPC, then progressed, and were treated with abiraterone asetate + prednisolon or enzalutamide in the second line.

Cases with <4 bone metastases, isolated lymph node metastases, or visceral metastases were excluded in their progression after docetaxel therapy. Cases with uncontrolled cardiac disease, uncontrolled diabetes requiring insulin use, or orthopedic disorder associated with permanent bone fracture were also excluded. In addition, cases who could not complete 6 cycles of 21-day docetaxel treatment for any reason were also excluded (Fig. 1). After applying

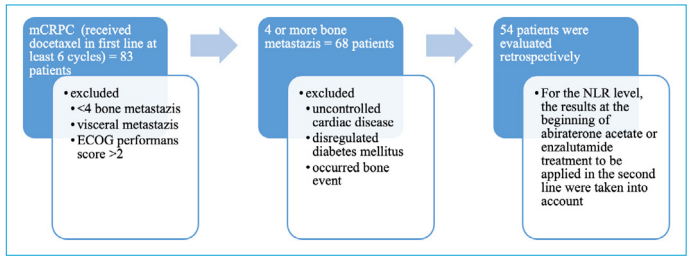

Figure 1. Flow chart.

the exclusion criteria, 54 cases were obtained and included in the retrospective analysis.

Exploratory analyzes were performed using Receiver Operating Characteristic (ROC) curves to estimate the optimal NLR threshold. The mean NLR was chosen as the cut-off threshold, as there was no strong evidence to suggest an optimal threshold from the ROC analyses.

The relationship between NLR and PFS was evaluated. The progression criterion was accepted as the time from initial PSA response to PSA progression under abiraterone or enzalutamide therapy. In addition, stratified analysis was performed according to whether NLR regression occurred in the first 6 weeks of treatment.

The planned primary endpoint of our study was; To analyze the relationship between NLR and PFS at the start of abiraterone acetate or enzalutamide treatment in mCRPC cases in progression after docetaxel, both as a correlation and as a bilayer according to the NLR threshold. Secondary endpoints were to examine the relationship between the presence of NLR regression at the sixth week of new-line therapy and PFS, and to evaluate the relationship between metastasis in the extremity bones and between NLR and PFS.

This study received approval from the Institutional Review Board of the University of Health Sciences Diyarbakır Gazi Yaşargil Research and Training Hospital to review archived patient records. Ethical committee approval was obtained (approval date 08.2020; approval number 547). This study was conducted in concordance with the principles of the Declaration of Helsinki.

The IBM Statistical Package for Social Sciences (SPSS®) v.23 was used for statistical analysis. Receiver operating characteristic curve analysis was performed to determine cut off values. Survival curves and rates were determined using the log-rank test and Kaplan-Meier analysis. Hazard ratios were determined using the Cox proportional hazards model and are reported with 95% confidence intervals. Univariate and multivariate analyses were based on the Cox proportional hazards model. Corelation analysis performed by Spearman method. A p-value of less than 0.05 was considered statistically significant.

Results

54 cases with a median age of 69 (54-75) years were evaluated. All cases are bone metastatic. All of the cases received at least 6 cycles of docetaxel treatment with the diagnosis of CRPC. A mean of 9.1 months of PFS occurred in the Docetaxel step. Twenty-five (46.3%) of the cases received abiraterone acetate+prednisolone and 29 (53.7%) received enzalutamide treatment. The Gleason score of 3 cases was 7 (5.6%), 18 cases (33.3%) score was 8, 33 (61.1%) cases score was 9. The demographic characteristics of the patients are given in Table 1.

The overall group mean NLR result is 3.34. The cases with NLR below 3.34 were determined as the low NLR group, and the cases above the NLR group were determined as the high NLR group. 31 cases (57.4%) were in the low NLR group, while 23 cases (42.6%) were in the high NLR group. The mean PFS of the high NLR group was 5.3 months, while the mean PFS of the low NLR group was 7.2 months, and the difference was statistically significant ($p<0.001$). A strong negative correlation was found between NLR level and PFS ($r=0.833$, $p<0.001$) (Table 2).

The groups were compared according to whether the NLR levels examined at the sixth week of abiraterone acetate+prednisolone or enzalutamide treatments showed regression with respect to the NLR levels at the beginning of the treatment. NLR regression occurred in 36 cases (66.7%). NLR regression could not be achieved in 18 cases (33.3%). The mean PFS was 7.0 months in the group with NLR regression, while the mean PFS was 5.2 months in the group without NLR regression, and there was a statistically significant difference between the two groups ($p<0.001$) (Table 2).

When the patients were divided into two groups according to the presence of extremity bone metastases, 18 cases (33.3%) had extremity bone metastases. No extremity bone metastasis was observed in 36 cases (66.7%). While the duration of PFS was 7.1 months in the group without extremity bone metastasis, it was 5.1 months in the group with extremity bone metastasis, the difference between the two groups was statistically significant ($p<0.001$). When the two groups were evaluated in terms of NLR levels, mean NLR was found to be 4.55 in the group with extremity bone metastasis, mean NLR was 2.74 in the group without extremity bone metastasis, again a statistically significant difference was observed ($p<0.001$) (Table 2).

When the PFS of first-line docetaxel treatments was compared with the low/high NLR groups; PFS was 7.3 months in the high NLR group and 10.5 months in the low NLR group, and there was a statistically significant difference between the two groups ($p=0.07$) (Table 2).

Table 1. Demographic features of patients

Cases (n)	54
Age	69 (54-75)
Gleason 7/8/9	3 (5.6%)/18 (33.3%)/33 (61.1%)
First line docetaxel pfs (mean, min-max)	9.1 (6-14)
Abirateron/enzalutamid (n,%)	25 (46.3%)/29 (53.7%)

Table 2. Main parameters taken into statistical evaluation

Mean nlr (whole group)	3.34
Low NLR/ high NLR (n,%)	31 (57.4)/23 (42.6)
Mean pfs low NLR (month)	7.2
Mean pfs high NLR (month)	5.3
p value	<0.001
Spearman analysis NLR and PFS	
r value	- 0.833
p value	<0.001
PFS of NLR regression group (n=36,66.7%) (month)	7
PFS of NLR stable or progression group (n=18,33.3%)	5.2
p value	<0.001
PFS relationship with precense of limb bone metastazis	
Present (n=20,37%)	7.1
Absent (n=34,63%)	5.1
p value	<0.001
First line docetaxel pfs relationship with nlr	
Mean PFS low NLR (month)	10.5
Mean PFS high NLR (month)	7.3
p value	=0.07
PFS – treatment type	
Abiraterone asetate+prednisolon (month)	6.4
Enzalutamide (month)	6.5
p value	=0.52

The mean PFS of those taking abiraterone acetate + prednisolone was 6.4 months, while the mean PFS of those taking enzalutamide was 6.5 months. There was no statistically significant difference in PFS according to the type of treatment received ($p=0.52$).

Discussion

While the prognostic value of the NLR level examined at the beginning of the treatment in various cancers is controversial, the level of evidence is higher in patients with mCRPC. With a better understanding of the predictive value of NLR, its importance in the selection of treatment in multi-option malignancies such as prostate cancer has increased.[5] In our study, it is seen that high NLR level in post-docetaxel setting predicts low PFS. The strong negative correlation

between NLR and PFS supports this statistical result.

NLR is measured from peripheral blood and is directly related to leukocyte activity in the tumor microenvironment. A high NLR level may be associated with low lymphocyte lineage activity, elevated myelocyte lineage activity, or both. Evidence that tumor-associated myelocytic cell activity has an impact on tumor proliferation and cancer progression through multiple mechanisms is increasing day by day.[9] Neutrophils may facilitate metastasis by suppressing CD8 T lymphocyte activity. In the pathogenesis of cancer, myeloid-associated suppressor cells create an immunosuppressive microenvironment.[10] Androgen deprivation therapy facilitates myeloid-associated suppressor cell infiltration over time. In this way, the production of interleukin 23 may contribute to the development of mCRPC.[11] There are studies on the association of cytotoxic chemotherapy-associated neutropenia or leukopenia with increased OS. In a novel study comparing docetaxel and mitoxantrone, OS benefit was shown in favor of docetaxel, while higher grade neutropenia was observed in docetaxel (58% vs 32%).[12] In the TROPIC study, while the benefit of OS was demonstrated with cabazitaxel, the relationship between the development of grade 3 neutropenia and the benefit of OS was revealed.[13] Based on these results, it can be speculated that the suppressed myelocytic activity in the course of cancer leads to increased OS with low NLR. Our study was based on the NLR, which was checked when transitioning to the next step after docetaxel treatment. When we look at the low NLR group, we see that the docetaxel PFS result they left behind is statistically significantly higher. This situation coincides with the results of myelocytic suppression and increased OS in cytotoxic chemotherapy studies in the literature in the diagnosis of mCRPC.

In terms of case demographics and clinical features, mCRPC represents a population predominantly of elderly and comorbid patients. Therefore, while conducting a clinical study, it is necessary to exclude linearly increasing risks related to age and heterogeneities that may develop due to disease burden as much as possible. Therefore, our study did not include patients with bone event or patients with visceral metastases. There is no significant heterogeneity in the patient group in terms of the Gleason score.

There are many studies evaluating patients who previously received abiraterone acetate+prednisolone or enzalutamide, and showing the association of high NLR with poor prognosis. Leibowitz-Amit et al. found that NLR levelshigher than 5 was associated with poor PSA response and resulted in low OS in abiraterone acetate+prednisolone treatment.[14] In a study conducted in mCRPC patients in the post-docetaxel setting, it was found that NLR above 3 was associated with poor enzalutamide response. While OS was 10.4 months in the NLR>3 group, it was 16.9 months in the NLR<3 group ($p<0.05$).[15] Boegemann et al. conducted, the relationship between high NLR and low OS was shown for abiraterone acetate+prednisolone treatment.[16] In a post hoc analysis of the COU-AA-302 study, an initial NLR of over 2.5 was found to be associated with short OS and PFS in abiraterone acetate+prednisolone treatment.[17]

When we look at the limitations of our study,first of all, our study design is retrospective, it would be more objective to conduct randomized controlled prospective studies on this subject. In addition, cross-sectional acquisition of NLR data is a limitation. An analysis that also evaluates NLR data before and during primary docetaxel therapy may yield more comprehensive results. In addition, it would be more beneficial if the study was carried out in a multicenter and with a larger number of patients.

In conclusion, in this study, we evaluated patients with a diagnosis of mCRPC who received abiraterone acetate + prednisolone or enzalutamide therapy after docetaxel chemotherapy. We determined the time to maintain NLR level as the start of abiraterone acetate + prednisolone or enzalutamide treatment. We concluded that NLR level above 3.34 and failure to achieve NLR regression in the first six weeks of treatment are poor prognostic factors. In addition, we believe that the presence of extremity bone metastases is associated with NLR and has a poor prognosis. We believe that NLR measurement, which is an inexpensive, practical and accessible method, will be useful in terms of prognostic prediction in cases with mCRPC diagnosed and receiving second or further line treatment. NLR levels may be a useful instrument to avoid overtreatment in elderly patients.

Disclosures

Ethics Committee Approval: This study received approval from the Institutional Review Board of the University of Health Sciences Diyarbakır Gazi Yaşargil Research and Training Hospital to review archived patient records. Ethical committee approval was obtained (approval date 08.2020; approval number 547). This study was conducted in concordance with the principles of the Declaration of Helsinki.

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