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Neutrophil-to-lymphocyte ratio predicts PSA response, but not outcomes in patients with castration-resistant prostate cancer treated with docetaxel

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Abstract
Purpose The neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammatory response and evidences for the relationship between NLR and the response to treatment gradually increases in cancer patients. In this study, we aimed to investigate the effect of the pretreatment NLR and other factors related to the patient on predicting the outcome of docetaxel + prednisone chemotherapy in prostate cancer patients who become castration resistant.
Materials and methods Thirty-three metastatic castration-resistant prostate cancer patients those who were treated between 2009 and 2013 were included in our study. All data of the patients, including pathological, clinical, radiological, biochemical and hematological data, were assessed retrospectively using our database system.
Results The median progression-free survival (PFS) was determined as 23.9 months (range 0.36–118.7) with androgen suppression therapy and 9.5 months (range 1.7–39.4) with docetaxel + prednisone therapy. NLR was found to be correlated with only posttreatment psa levels. In the NLR ≤ 3 group, the PSA levels were statistically significantly lower than the other group ($r = 0.002$). Furthermore, the relationships between the clinical response and PFS and the other pretreatment parameters of the patients were evaluated in order to predict which group would respond better to docetaxel + prednisone therapy after becoming androgen resistant. No relationship was found between any of the parameters and the response to therapy.
Conclusion Although NLR was found effective in predicting the PSA response in docetaxel + prednisone therapy, neither NLR nor any other clinical parameter was found effective in predicting the outcome and the role of NLR in the future of CRPC is questionable.

Keywords Castration-resistant prostate cancer · Neutrophil-to-lymphocyte ratio · Docetaxel + prednisone

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Introduction

As it is the most common cancer among men and the second leading cause of cancer-related death, prostate cancer is a significant oncological public health problem [1]. Although prostate cancer can be detected at earlier stages and curative treatment modalities may be used, many present at the metastatic stage. After androgen suppression therapy, most of the patients eventually progress into castration-resistant state and the use of cytotoxic chemotherapy is compulsory. Docetaxel has been widely used as the first-line chemotherapeutic agent after its efficacy was shown in a randomized phase III trial [2]. However, no robust biochemical or clinical marker has been defined as predictive marker for docetaxel chemotherapy to date. Recent studies have shown that a tumor-induced inflammation is related to local tissue damage caused by growth and invasion of the tumor [3–6]. Cancer-

induced inflammatory response and associated inflammatory markers have been considered as being prognostic and predictive in gastric cancer patient [7, 8]. Neutrophile–lymphocyte ratio (NLR) is an easy, cheap and reproducible indicator [5, 9–12] and has been reported as a poor prognostic factor in several cancers including colon, bladder, stomach cancers and glioblastoma multiforme [8, 9, 13–15]. We do not know its predictive and prognostic value in metastatic castration-resistant prostate cancer. In this study, we aimed to investigate the relationship between pretreatment NLR, treatment response, and the other clinical and pathological parameters in castration-resistant prostate cancer patients.

Materials and methods

Thirty-three metastatic castration-resistant prostate cancer patients who were treated with docetaxel chemotherapy in our center between 2009 and 2013 were included in our study. The patients with active infection, history of inflammatory disease or medication that might affect hematological parameters were excluded. Eastern Cooperative Oncology Group Performance Score (ECOG-PS), findings from physical examination, radiological, biochemical and hematological parameters were obtained from the medical records retrospectively. All patients included in the study received docetaxel 75 mg/m^2 every 21 days and 5 mg prednisolone twice daily/everyday. All patients continued to receive the LHRH analogue during systemic chemotherapy. Patients with bone metastases received biphosphonate if there was no contraindication.

Response evaluation

All data were analyzed retrospectively. Progression-free survival (PFS) was assessed separately before and after the patient became androgen resistant. For radiological response evaluation, Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) [16] was used. Progression was defined as radiological progression by RECIST 1.1 and/or an increase of more than 25 % or 2 ng/ml in PSA values in comparison with the pretreatment PSA value.

Statistical analyses

All descriptive statistics were carried out using Mann–Whitney Test and Fisher's exact test. NLR cutoff value was considered as the most significant p value in survival obtained from the review of the analyses of previous studies using logrank test [14]. The relationship between the parameters of the patients was assessed using Spearman's correlation test. Kaplan–Meier method was used to assess the relationship between NLR and PFS. Logrank (Mantel–Cox) method was performed to evaluate the effect of the parameters on survival. All of the data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA), and a two-sided p value of ≤ 0.05 was considered statistically significant.

Table 1 Baseline patient characteristics

Parameter	Value
Age at the initiation of chemotherapy (years, mean ± sd)	71.24 ± 7.34
ECOG-PS value before chemotherapy	
ECOG 0	1 (3 %)
ECOG 1	25 (75.8 %)
ECOG 2	7 (21.2 %)
Combined Gleason score (%)	
Low risk (≤6)	2 (6.1 %)
Intermediate risk (7)	5 (15.2 %)
High risk (8–10)	21 (63.6 %)
Primary treatment *n* (%)	
Radical prostatectomy	0
Radiation therapy	1 (3 %)
Primary androgen deprivation therapy	32 (97 %)
Locations of metastases at the time of diagnosis (%)	
Bone alone	25 (75.8 %)
Lymph node	1 (3 %)
Multiple metastases	7 (21.2 %)
PFS on androgen suppression therapy (months)	23.96 (range 0.36–118.79)
PFS after becoming androgen-resistant PFS (months)	9.51 (range 1.77–39.44)
Leukocyte count/mm^3 (mean ± sd)	7,733 ± 2,628
Neutrophil count/mm^3 (mean ± sd)	5,174 ± 2,143
Lymphocyte count/mm^3 (mean ± sd)	1,593 ± 849
Hemoglobin gr/dl (mean ± sd)	11.42 ± 1.45
Basal PSA ng/ml (mean ± sd)	338.38 ± 482.1
Neutrophil-to-lymphocyte ratio (mean ± sd)	4.23 ± 2.95

Results

Included were 33 patients with a mean age of 71.24 ± 7.34. ECOG-PS was determined as 0, 1 and 2 in 1 (3.0 %), 25 (75.8 %) and 7 patients (21.2 %), respectively. (ECOG-PS 0—Asymptomatic, 1—Symptomatic but completely ambulatory, 2—Symptomatic, <50 % in bed during the day, 3—Symptomatic, >50 % in bed, but not bedbound, 4—Bedbound, 5—Death) The mean Gleason score was 8.42 ± 1.03. Metastatic sites were isolated bone metastases, lymph node metastasis and visceral metastases in 25 patients (75.8 %), 1 patient (3.0 %) and 7 patients (21.2 %), respectively. No

Table 2 The relationships between neutrophil-to-lymphocyte ratio and the parameters of the patients

Parameter	*p* value
Clinical response	Non significant
Overall PFS	Non significant
PFS after chemotherapy	Non significant
Overall survival	Non significant
PSA levels after treatment	0.002

PFS progression-free survival, *PSA* prostate-specific antigen

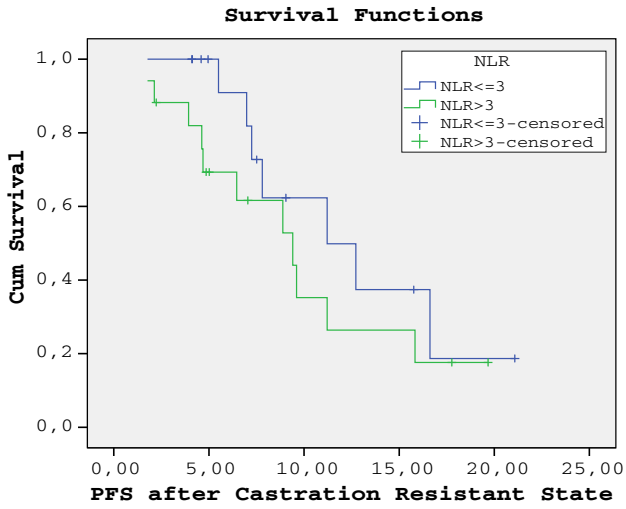

Fig. 1 Progression-free survival interval by NLR groups

patient had a history of curative radical prostatectomy or radical radiotherapy except one. The mean pretreatment leukocyte count, neutrophil count, lymphocyte count and hemoglobin values were 7,733 ± 2,628, 5,174 ± 2,143, 1,593 ± 849 and 11.42 ± 1.45, respectively. The mean value for pretreatment and posttreatment PSA value were 338.38 ± 482.1 and 165.01 ± 373.92. The mean value for NLR was determined as 4.23 ± 2.95, and the cutoff value was accepted as 3. By using this cutoff value, study group was divided into two groups; 15 patients with pretreatment NLR ≤3 (45.4 %) formed one group and 18 patients with NLR >3 formed other group (54.6 %). Basal demographic characteristics of these groups were summarized in Table 1. In whole group, the median PFS was 23.9 (range 0.36–118.7) and 9.5 months (range 1.7–39.4 months) at castration sensitive and resistant states, respectively. No complete response was achieved. Stable disease and partial response were achieved in 4 patients (13.2 %) and 21 patients (63.6 %) while 8 patients had progressive disease (26.4 %).

There was a significant correlation between NLR and posttreatment PSA levels. The PSA levels in the NLR ≤3 group were significantly lower than other group ($r = 0.002$). Whole findings were summarized in Table 2. The PFS according to the NLR value after becoming androgen resistant was shown in the Fig. 1. In addition, to the clinical response and PFS, other pretreatment parameters (age, combined Gleason score, primary treatment, ECOG-PS, duration of response to prior ADT ≥12 months, basal psa, sites with disease involvement, anemia, pretreatment NLR) were analyzed in order to predict which patient group would respond better to docetaxel + prednisone treatment. Any correlation was not found between and the response to docetaxel + prednisone treatments according to the results. The findings were summarized in Table 3.

Table 3 Association between clinicopathologic and prognostic factors and chemotherapy-related progression-free survival interval

Parameter	Univariate analysis
Age	Non significant
Combined Gleason score	Non significant
Primary treatment	Non significant
ECOG performance score	Non significant
Duration of response to prior ADT ≥12 months	Non significant
Basal PSA	Non significant
Sites with disease involvement	Non significant
Anemia	Non significant
Pretreatment NLR	Non significant

ADT androgen deprivation therapy, *PSA* prostate-specific antigen, NLR neutrophil–lymphocyte ratio, *ECOG-PS* eastern cooperative oncology group performance score

Discussion

Prostate cancer is an old man disease, and maintaining the quality of life is one of the main goals as improving survival parameters. Therefore, predictive markers are particularly important to avoid unnecessary drug toxicity in this group of patients. These predictive markers can be various hematological, biological and molecular markers; for example, circulating tumor cells at baseline and posttreatment is prognostic of survival and predictive to some treatment modalities in metastatic and castration-resistant prostate cancer in different studies [17, 18].

In this study, we tried to investigate possible predictive role of NLR in patients with castration-resistant prostate cancer those who were treated with docetaxel chemotherapy. Our findings for toxicity and response rates were consistent with literature.

The role of the immune system has been well defined in multistep carcinogenesis process [4–7, 19–21]. NLR,

which is accepted as an actual marker of inflammation, has been tested as predictive and prognostic marker during the recent years, along with the other clinical parameters of the patients [5, 10, 11, 13, 22, 23]. Keizman et al. investigated the relationship between the pretreatment NLR along with clinical parameters and response rate in 156 patients with castration-resistant prostate cancer under ketoconazole treatment. This study showed that the patients with NLR $\leq$3 had significantly higher response rate than the patients with NLR >3 (p: 0.01) [9]. The patients had limited disease, late recurrence after former treatment longer than 24 months and PSA doubling time longer than 3 months. In our study, we showed reduction in the PSA levels in the NLR $\leq$3 group was significantly higher than NLR >3 group. However, statistical analysis failed to show no significant relation between NLR and other clinical parameters. Lower NLR values may be associated with a stronger lymphocyte-mediated immune response against the tumor as a result of relatively higher counts of lymphocytes in comparison with neutrophil count and less aggressive tumor biology as a consequence of abnormal cytokine discharge related to neutrophils [5]. We believe that the demonstration of this situation in the presence of an impacted immune system due to cytotoxic chemotherapy added extra value to this study. In literature, there are some studies which suggest NLR might be used as a prognostic marker in glioblastoma, colon, bladder and prostate cancer patients [8, 13–15]. However, there is no study on predictive and prognostic role of NLR in castration-resistant prostate cancer patients. Limitations of our study were retrospective design, small and underpowered sample size, being a unicentric study and treatment heterogeneity in first-line treatment modalities.

In this study, we try to investigate possible predictive role of pretreatment NLR in castration-resistant prostate cancer. We suggest that this may help us to make more precise decision for chemotherapy usage in this fragile patient group. Although present study showed that there is statistically significant relation between PSA response and NLR value, univariate analysis failed to show any significant effect of NLR or other clinicopathological markers on PFS for docetaxel + prednisone therapy. This result can be associated with the underpower size of our study. So before making exact suggestions for predictive markers in patients with castration-resistant prostate cancer those who were treated with docetaxel chemotherapy + prednisone therapy, prospectively designed, big sample-sized multicenter studies are needed.

In conclusion although NLR was found effective in predicting the PSA response in docetaxel + prednisone therapy, neither NLR nor any other clinical parameter was found effective in predicting the outcome and the role of NLR in the future of CRPC is questionable.

Conflict of interest The authors of this manuscript have no conflicts of interest to disclose. The authors have full control of all the primary data and agree to allow the journal to review the data if requested.

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