Neutrophil-to-lymphocyte ratio as a prognostic marker in highly PD-L1 expressing advanced non-small cell lung cancer patients in first line treatment with pembrolizumab

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ABSTRACT

Introduction and objectives: The neutrophil-lymphocyte ratio (NLR) has been proposed to assess advanced stage non-small cell lung cancer (aNSCLC) response to immunotherapy, given the easy availability and low cost. The aim of our study was to evaluate the relationship between NLR at baseline, after the 3rd and 6th treatment cycles, and progression free survival (PFS) and overall survival (OS), in a population with aNSCLC with a PD-L1 expression ≥50% treated with pembrolizumab monotherapy in first line.
Methods: We performed a retrospective study of patients with aNSCLC with PD-L1≥50% who were treated with pembrolizumab first line from February 2017 to July 2021. NLR values at baseline and after the 3rd and 6th pembrolizumab cycles were analyzed. Optimal NLR cut-off were determined with respect to OS, by ROC curve. PFS and OS were compared by Kaplan Meyer method and Cox Proportional Hazard model for NLR measures.
Results: Sixty-six patients with PD-L1≥50% (51% males, mean age 65.8 ± 11.2 years) were included in the study. The PD-L1 expression was ≥90% in 74% of the patients. NLR≤4 after the 3rd pembrolizumab cycle were associated with a significant improvement in PFS (23.6 vs 4.3 months, p=0.002) and OS (32.9 vs 6.3 months, p=0.022), compared with NLR>4.
Discussion and conclusions: In patients with aNSCLC and a PD-L1≥50% receiving frontline pembrolizumab treatment, low NLR values after the 3rd pembrolizumab cycle were associated with significantly longer PFS and OS. This biomarker may thus help identify individuals on pembrolizumab monotherapy who are at greatest risk for disease progression.

Keywords: Lung cancer, pembrolizumab, PD-L1, neutrophil-lymphocyte ratio, Non-small Cell Lung Cancer (NSCLC)

INTRODUCTION

Lung cancer is the second most common malignancy worldwide and is responsible for the highest mortality burden [1]. In recent years, the use of Immunotherapy revolutionized the clinical practice and treatment of advanced stage non-small cell lung cancer (aNSCLC). The anti-programmed cell death protein 1 (anti-PD-1) pembrolizumab alone in first line showed a 3-year overall survival (OS) of 43.7% as opposed to an OS of 24.9% in chemotherapy-treated patients. Pembrolizumab monotherapy has become the recommended treatment for patients with aNSCLC and a programmed cell death-ligand 1 (PD-L1) tumor expression of at least 50% [2].

PD-1, also called immune checkpoint molecule, is a transmembrane protein presented in macrophages, dendritic cells and T and B lymphocytes. When the PD-1 molecule binds to one of its ligands expressed in human tumour cells (PD-L1 and PD-L2), cytotoxic T cell response is inhibited, bypassing the body's immune response against tumour cells [3,4].

PD-L1 expression has been used as a predictor of response to pembrolizumab treatment, however, variability in response to therapy has been observed regardless of the high PD-L1 expression (≥50%). This may be related to the PD-L1 antibodies variety, intra-tumour PD-L1 expression heterogeneity, and the molecular diagnostic methods used [5]. Thus, several studies have emerged trying to identify markers to predict response to immunotherapy. Peripheral markers such as the neutrophil-lymphocyte ratio (NLR) have been proposed to assess this response, given their easy availability and low cost [6-12]. In cancer, tumour associated neutrophils play as regulators of the tumour microenvironment, promoting stromal remodelling, angiogenesis, metastasis, thrombosis, and impairment of T-cell-dependent antitumor immunity [13,14]. High NLR values are associated with low survival and lower probability of response to immunotherapy in advanced stages of several types of cancer [6-8,12].

In NSCLC, high NLR prior to treatment in general has been shown to be an indicator of poor prognosis [11,15,16]. In PD-L1 ≥50% aNSCLC treated with pembrolizumab, high pre-treatment NLR has been associated with worse outcomes. Some studies have also revealed that high NLR values after a few weeks of pembrolizumab treatment can predict the response to immunotherapy and consequently the prognosis [17-19]. However, there is a highly variability of the NLR cut-off used in different studies [9,10].

We therefore performed a retrospective study to evaluate the relationship between NLR at baseline (NLR-T0), after the 3rd (NLR-C3) and 6th treatment cycles (NLR-C6), and the progression free survival (PFS) and OS, in a population with aNSCLC with a PD-L1 expression ≥ 50% treated with pembrolizumab monotherapy in first line. We also compared patients' clinical data, tumor characteristics (histology, PD-L1 expression), pembrolizumab toxicity between low and high NLR groups and its association with OS.

MATERIAL AND METHODS

We performed a retrospective study based on the analysis of data obtained from the medical records of all the patients with aNSCLC with no identification of oncogenic drivers who were treated in the Pulmonary Oncology Unit of the Centro Hospitalar e Universitário de Coimbra (CHUC), Portugal, between February 2017 and July 2021. The inclusion criteria were the patients aged more than 18 years, with diagnosis of aNSCLC accord-

ing to international guidelines, with a tumour expression of PD-L1 ≥50%, that received first line treatment with pembrolizumab in monotherapy. The exclusion criteria were prior diagnosis of other cancer, or patients previously treated for primary NSCLC. This study was approved by the Ethics Commission of Centro Hospitalar e Universitário de Coimbra.

Pembrolizumab was administered at a dose of 200mg, intravenously every 3 weeks until progression, intolerance, patient's decision to stop or for 35 cycles, as per institutional treatment protocols.

Clinical data

Clinical data concerning the patient (age, gender, ECOG Performance Status, smoking status) and their disease (histology, staging, location of the metastases when present) were extracted from electronic medical records of the patients. The data concerning the treatment and follow-up of the patients were also analysed (incidence, severity, and adverse events related to immunotherapy (iAE), disease progression or and death). Diagnosis of iAE was based on the treating healthcare practicians assessment.

Blood tests

Complete blood count with leucogram at the day of pembrolizumab initiation, after the 3rd and 6th cycles (right before 1st, 4th and 7th treatment cycles, respectively) were obtained from electronic medical records. NLR ratio were defined as absolute neutrophil count/absolute lymphocyte count.

PD-L1 expression

PD-L1 tumour expression was assessed using Dako 22C3 antibody by immunohistochemistry (IHC) in tumour samples.

Clinical endpoints

PFS was defined as the time elapsed from the date of aNSCLC diagnosis until the date of physician determined progression. Tumour progression was assessed by the Response Evaluation Criteria in Solid Tumours (RECIST) criteria version 1.1 [20]. OS was defined as the time elapsed from the date of aNSCLC diagnosis until the date of death.

Statistics

Quantitative data with a normal distribution was expressed as mean and standard deviation (SD) and data without normal distribution were expressed as median and interquartile range (P25-P75). Continuous variables differences were determined by *t*-test for normal distribution and those with non-normal distribution by nonparametric Mann-Whitney test. The χ^2 test was used to compare categorical variables. Receiver operating characteristic curves (ROC curves) were performed to analyse discrimination capability by the area under the curve (AUC), and NLR-T0, NLR-C3 and NLR-C6 optimal cut-offs were identified. Event-time distributions were evaluated using the Kaplan-Meier method and compared with log-rank test. Univariate and multivariate Cox regression analysis was used to estimate hazard ratios (HR) and corresponding 95% confidence interval (95% CI) for patients' variables and OS. A *p* value less than 0.05 was considered statistically significant. Statistical analysis was performed by using SPSS 26.0 software.

RESULTS

A total of 66 subjects with aNSCLC and a PD-L1 expression greater than 50% treated in the in Centro Hospitalar e Universitário de Coimbra with

pembrolizumab monotherapy in first line were included in this study and their characteristics are described in detail in Table 1. The mean age of participants was 65.8 ± 11.2 years and 51% were male patients. About a third of participants were never smokers. According to the histology, 65.2% patients had adenocarcinoma and 27.3% had squamous carcinoma. The PD-L1 expression was 90% or more in 74% of patients. Metastasis were present in 89.4% of the patients and 81.8% presented a performance status of 0 or 1. In all subjects, the median values of NLR-T0, NLR-C3 and NLR-C6 were 4.0 ± 4.0, 3.0 ± 3.9 and 2.6 ± 2.8, respectively.

Table 1. Patient characteristics at baseline

Patient Characteristics	Total sample (n=66)
Age at aNSCLC diagnosis, mean (SD)	65.8 (11.2)
Gender	
Male, n (%)	51 (77.3)
Female, n (%)	15 (22.7)
ECOG PS	
0-1, n (%)	54 (81.8)
2-3, n (%)	12 (18.2)
Smoking status	
Current, n (%)	41 (62.1)
Former, n (%)	5 (7.6)
Never, n (%)	20 (30.3)
Tumor histology	
Adenocarcinoma, n (%)	43 (65.2)
Squamous, n (%)	18 (27.3)
Adenosquamous, n (%)	2 (3.0)
Pleomorphic, n (%)	2 (3.0)
Bigger cells, n (%)	1 (1.5)
Initial Stage	
III, n (%)	7 (10.6)
IV, n (%)	59 (89.4)
PD-L1 expression	
≥90% n (%)	17 (25.8)
50-89% n (%)	49 (74.2)
NLR	
NLR-T0, median (IQR)	4.0 (4.0)
NLR-C3, median (IQR)	3.0 (3.9)
NLR-C6, median (IQR)	2.6 (2.8)

Toxicity to pembrolizumab occurred in 39 patients (59.1%), but treatment discontinuation was necessary in only 12 cases. Other reasons to stop pembrolizumab were disease progression, death and completed treatment in 23, 12 and 2 patients, respectively. Population mortality was 53% (n=35). Median PFS and OS in study sample were 8.9 months (95% CI 1.1-16.8) and 21.2 months (95% CI 11.7-30.4).

Concerning discriminative capacity to predict death, the ROC curve analysis showed that NLR at baseline and after the 3rd cycle provided a satisfactory (AUC 0.67, $p<0.05$) and good (AUC 0.73, $p<0.05$) performance. NLR at baseline and after the 3rd cycle provided also a satisfactory (AUC 0.68, $p<0.05$) and good (AUC 0.73, $p<0.05$) performance in predicting disease progression, respectively. NLR after the 6th cycle showed no discriminative capacity to predict death (AUC 0.69, $p>0.05$) or disease progression (AUC 0.64, $p>0.05$). Based on the ROC curve, the median value (4.0) was used as the cut-off value to classify each patient as high-NLR (more than 4.0) or low-NLR (4.0 or less) in further survival analysis.

The relation of NLR-T0 and NLR-C3 values with baseline clinicopathologic characteristics and clinical outcomes are observed in Table 2. After the 3rd cycle of pembrolizumab, patients with high NLR levels (NLR>4 vs NLR≤4) were more likely to have progression of disease and death ($p<0.05$).

At baseline, patients with low NLR levels (NLR≤4) demonstrated a longer PFS (median 21.7 vs 4.4 months, $p>0.05$) and OS (32.9 vs 11.1 months, $p>0.05$) compared with high NLR values (NLR>4), however this increase was not statistical significant. After the 3rd pembrolizumab cycle, low NLR values (NLR≤4) were associated with a significant improvement in PFS (23.6 vs 4.3 months, $p=0.002$) and OS (32.9 vs 6.3 months, $p=0.022$) compared with high NLR values (NLR>4) (Figure 1).

Table 2. Patient characteristics stratified by NLR values at baseline and after 3rd pembrolizumab cycle

Patient Characteristics	Baseline			After 3rd pembrolizumab cycle		
	NLR_T0 ≤4 N=29	NLR_T0 >4 N=36	P value	NLR_C3 ≤4 N=32	NLR_C3 >4 N=14	P value
Age at aNSCLC diagnosis, mean (SD)	64.7 (9.3)	66.5 (12.8)	>0.05	64.5 (9.6)	67.7 (11.1)	>0.05
Gender						
Male, n (%)	23 (79.3)	27 (75.0)	>0.05	27 (84.4)	8 (57.1)	>0.05
Female, n (%)	6 (20.7)	9 (25.0)		5 (15.6)	6 (42.9)	
ECOG PS						
0-1, n (%)	25 (86.2)	29 (80.6)	>0.05	29 (90.6)	12 (85.7)	>0.05
2-3, n (%)	4 (13.8)	7 (19.4)		3 (9.4)	2 (14.3)	
Smoking status						
Current, n (%)	17 (58.6)	23 (63.9)	>0.05	18 (58.6)	1 (50.0)	>0.05
Former, n (%)	11 (37.9)	9 (25.0)		13 (40.6)	5 (35.7)	
Nonsmoker, n (%)	1 (3.4)	4 (11.1)		1 (3.1)	2 (14.3)	
Tumor histology						
Adenocarcinoma, n (%)	18 (62.1)	25 (69.4)	>0.05	20 (62.5)	13 (92.9)	>0.05
Squamous, n (%)	9 (31.0)	8 (22.2)		8 (25.0)	1 (7.1)	
Others, n (%)	2 (6.9)	3 (9.7)		4 (12.5)	0	
Initial Stage						
III, n (%)	4 (13.8)	3 (8.3)	>0.05	4 (12.5)	0	>0.05
IV, n (%)	25 (86.2)	33 (91.7)		28 (87.5)	14 (100)	
PD-L1 expression						
≥90% n (%)	6 (20.7)	10 (27.8)	>0.05	9 (28.1)	2 (14.3)	>0.05
50-89% n (%)	23 (79.3)	26 (72.2)		23 (71.9)	12 (85.7)	
Adverse effect of immunotherapy (iAE)	19 (65.5)	19 (52.8)	>0.05	18 (56.3)	10 (71.4)	>0.05
Disease progression	15 (23.1)	26 (40.0)	>0.05	11 (34.4)	11 (78.6)	0.006
Mortality, n (%)	12 (44.6)	22 (55.4)	>0.05	7 (21.9)	8 (57.1)	0.038

On univariate analysis the following covariates were associated with worse OS: ECOG PS of 2 or more (HR: 3.31, 95% CI: 1.48-7.42, p=0.003) and the NLR value after the 3rd pembrolizumab cycle (HR: 3.12, 95% CI: 1.12-8.72, p=0.03). Present or past smoking habits were associated with longer OS (HR: 0.33, 95% CI: 0.12-0.86, p=0.02). On multivariate analysis the following covariates were associated with poorer OS: adverse effect of immunotherapy (iAE) (HR: 4.98, 95% CI: 1.34-18.61, p=0.017) and high NLR value after the 3rd pembrolizumab cycle (HR: 3.91, 95% CI: 1.30-11.73, p=0.015).

As in the univariate analysis, present or past smoking habits were associated with longer OS on multivariate regression (HR: 0.12, 95% CI: 0.03-0.51, p=0.005). All results are presented on Table 3.

DISCUSSION

In this observational study of patients with aNSCLC and a PD-L1 expression greater than 50% receiving frontline pembrolizumab, we showed that subjects with low NLR values after the 3rd pembrolizumab cycle had an improved PFS and OS compared with high NLR values group. After adjusting for potential confounders, we demonstrated

Figure 1. Survival curves – primary lung cancer.

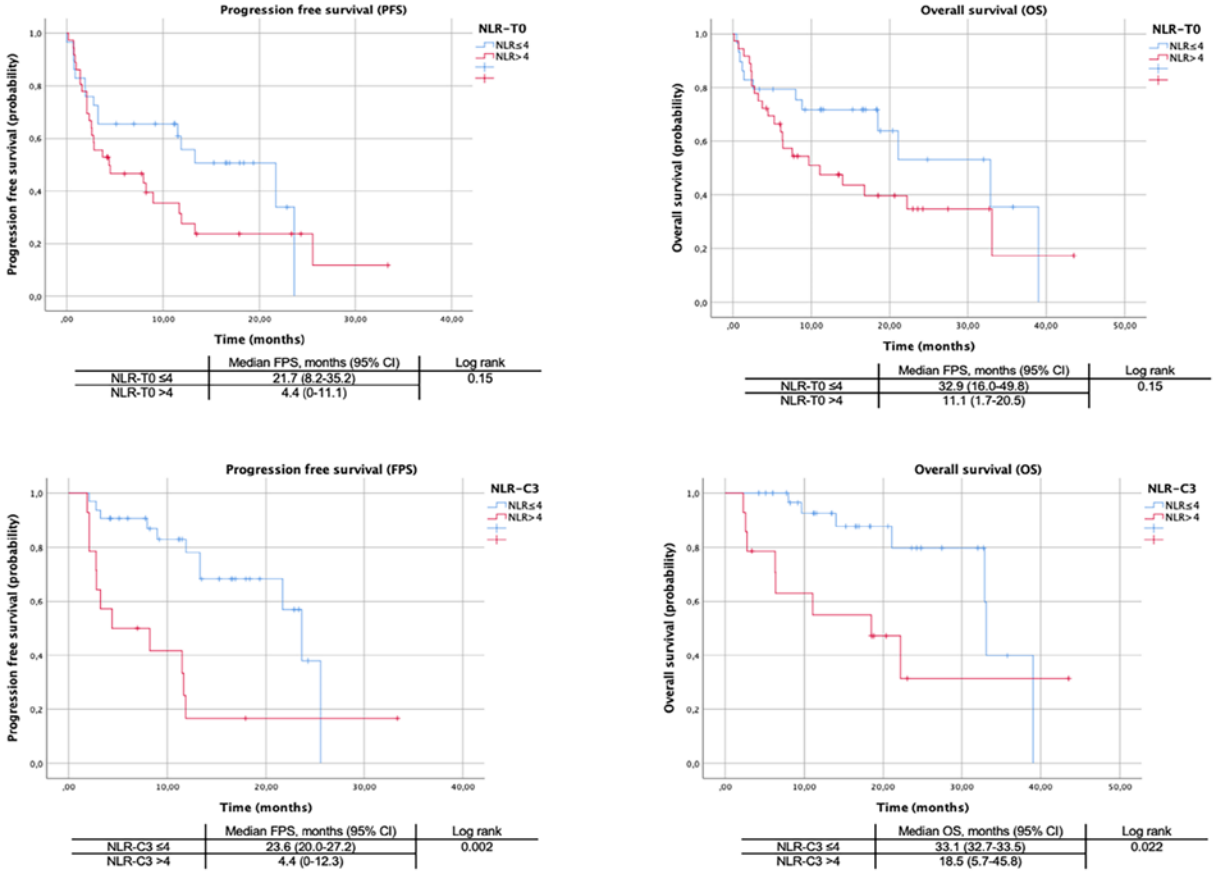

Table 3. Univariate and multivariate Cox regression analysis of OS with NLR values at baseline and after the 3rd pembrolizumab cycle

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.01 (0.98-1.05)	0.43		
Gender (male vs female)	1.63 (0.80-3.30)	0.17		
Smoking status (current/former vs never)	0.33 (0.12-0.86)	0.02	0.12 (0.03-0.51)	0.005
PD-L1 (≥90% vs <90%)	1.18 (0.54-2.58)	0.67		
ECOG PS (≥2 vs <2)	3.31 (1.48-7.42)	0.003	5.33 (0.91-31.13)	0.06
Adverse effect of immunotherapy (iAE) (present vs none)	1.83 (0.90-3.72)	0.09	4.98 (1.34-18.61)	0.017
NLR_T0 (>4 vs ≤4)	1.67 (0.82-3.38)	0.16		
NLR_C3 (>4 vs ≤4)	3.12 (1.12-8.72)	0.03	3.91 (1.30-11.73)	0.015

that NLR values >4 after the 3rd pembrolizumab cycle had almost 4-fold greater risk of death (all-cause mortality) (HR: 3.91, 95% CI: 1.30-11.73, p=0.015), compared with patients with NLR values less than 4. There was no difference in PFS and OS between high and low NLR levels at baseline and after 6th pembrolizumab cycle.

Although several studies have shown that high baseline NLR values are associated with worse PFS and OS outcomes in first line pembrolizumab treatment, there are fewer studies evaluating the importance of high NLR values during treatment. In our study we demonstrated the differences of OS and PFS in patients with high NLR values vs. low NLR values after a few treatment cycles. Similarly, Ayers *et al*. showed that an increase in the NLR between baseline and 2-8 weeks or 4-14 weeks after immunotherapy showed modestly significant correlation with lack of response in aNSCLC [19]. They further observed that sustained high NLR after initiation of treatment had a more profound impact on survival than baseline NLR, regardless of PD-L1 status. One meta-analysis showed that elevated blood NLR pre- and post-treatment was associated with significantly shorter OS and PFS in patients with NSCLC receiving PD-1/PD-L1 inhibitors [7].

The results of our study support previous published results and have clinical implications in that a sustained high level of NLR is particularly detrimental to patient outcomes and may help identify individuals who are at greatest risk for disease progression on pembrolizumab monotherapy prior to radiological assessment. Because this biomarker is readily available as part of the routine blood analysis of patients with cancer, application in the clinical practice would be easy and there would be no additional costs. Moreover, radiographic evaluation of treatment responses can be heterogeneous in immunotherapy, and atypical treatment response patterns termed pseudoprogression have been observed. Thus, blood markers after the 3rd pembrolizumab cycle (around 9 weeks after treatment initiation) may further assist in clarifying patient status for situations in which the radiologic findings are inconclusive [21].

The elevation of neutrophil values and consequently the NLR values after a few cycles of immunotherapy seems to reflect the levels of tumor associated neutrophils and thus the response to treatment, however the relationship between neutrophil counts of peripheral blood and tumor associated neutrophils is unclear.

We also demonstrated that presence of current or past smoke habits were associated with longer OS (HR: 0.33, 95% CI: 0.12-0.86, p=0.02). This finding was consistent with a previous meta-analysis that showed that either immunotherapy alone or in association with chemotherapy was less effective in never smokers, and with a recent study with first line pembrolizumab monotherapy in aNSCLC that reported consistently longer OS in current or former smokers [22,23]. This might be due to the high tumor mutational burden in patients with smoke habits compared with nonsmokers in subjects with lung cancer, which may make smoking induced lung cancer more sensitive to immunotherapy [22,24].

This study has some limitations that need to be considered. It was a single center experience with a retrospective observational design and with a limited sample size. In a future prospective study, the sample size should be calculated to detect an expected difference at the time of planning.

CONCLUSIONS

In conclusion, in patients with aNSCLC and a PD-L1 expression greater than 50% receiving frontline pembrolizumab treatment, low NLR values after the 3rd pembrolizumab cycle were asso-

ciated with significantly longer PFS and OS. This biomarker may thus help identify individuals on pembrolizumab monotherapy who are at greatest risk for disease progression.

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