Platelet-to-Lymphocyte Ratio as an Indicator to Predict Decreased Carbon Monoxide Diffusion of the Lung in Patients with Testicular Cancer

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ABSTRACT

Objective: To investigate whether the use of diffusing capacity of the lungs for carbon monoxide (DLCO) and neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) could be used to predict bleomycin-induced pulmonary toxicity in patients with testicular cancer (TCa).

Study Design: Descriptive study.

Place and Duration of Study: Ankara Oncology Training and Research Hospital, Turkey, between 2017 and 2020.

Methodology: Data of 40 patients with TCa, who were followed at cancer centre from 2017-2020 and received 3-4 cycles of BEP protocol were retrospectively screened and included who met the criteria for inclusion in the study. All patients with TCa, who were older than 18 years of age and had no secondary malignancy and comorbidity, were included in this study.

Results: A statistically significant negative correlation was found between DLCO change and NLR, PLR (r:-0.558, p:0.002 for NLR; r:-0.462 p:0.012 for PLR). A statistically significant positive correlation was found between DLCO change and lymphocyte level (r:0.436, p:0.018). The NLR and PLR were statistically higher in the group with a decrease of ≥10% in DLCO compared to the group with no decrease or a decrease of ≤10% in DLCO (for NLR; 3.03 ± 1.45 and 1.68 ± 0.73, respectively, p = 0.005; for PLR 187.72 ± 66.90 and 124.72 ± 47.99, respectively, p = 0.008). Multivariate regression analysis showed a statistically significant relationship between PLR increase and a decrease of ≥10% in DLCO.

Conclusion: PLR and LDH could be used as independent predictive biomarkers for DLCO decline which is used to identify bleomycin-induced pulmonary toxicity.

Key Words: *Bleomycin, Markers of inflammation, Platelet-to-lymphocyte ratio (PLR), Pulmonary diffusing capacity, Testicular cancer.*

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INTRODUCTION

Testicular cancer (TCa) is the most common solid tumor in men aged 20-34 and its incidence has been increasing in recent years.[1] A high success rate is achieved when bleomycin is combined with cisplatin and etoposide in the standard chemotherapy protocol. The most serious complications of bleomycin are pulmonary toxicity, which might present as pulmonary fibrosis or pneumonitis, observed in 3-20% of patients and leading to mortality in upto 1-3% of recipients.[2-4]

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The pulmonary toxicity of bleomycin occurs in two stages. At the initial stage, neutrophils, lymphocytes and macrophages accumulate in the interstitial and alveolar regions. In the second stage, reactive oxygen molecules and proteases, as well as fibrosis-mediated damage and initiation of a repair process for this damage occur in the pulmonary interstitial tissue.[2,5]

Reports showed decreases in total lung capacity (TLC) forced vital capacity (FVC) and the diffusing capacity of the lungs for carbon monoxide (DLCO).[6,7] The DLCO parameter is used to determine the risk of pulmonary toxicity caused by bleomycin exposure and to monitor toxicity.[8] It can be claimed that DLCO is the most sensitive indicator of subclinical pulmonary damage;[6] however, it is also reported to have low specificity.[9]

Previous studies have identified various risk factors for bleomycin-induced pulmonary toxicity, including advanced age, low body mass index (BMI), renal failure, cumulative and bleomycin dose.[2,4,10] The role of fibrosis in bleomycin-induced

pulmonary toxicity is important and inflammation plays a key role in pulmonary fibrosis.[11] In recent years, inflammation-based scoring systems created from routine blood parameters have gained acceptance as biomarkers in various conditions.[12,13]

The objective of this study was to investigate whether the combined use of DLCO and pulmonary function tests (PFTs), and markers obtained from blood counts, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), could be used to predict bleomycin-induced pulmonary toxicity.

METHODOLOGY

Data of 40 patients with TCa, who were followed at Ankara Oncology Training and Research Hospital from 2017-2020 and received 3-4 cycles of BEP protocol (bleomycin 30 mg per day 1, 8, 15/21, cisplatin 20 mg/m^2 per day 1-5/21, etoposide 100 mg/m^2 per day1-5/21) were retrospectively screened; and all patients with TCa, who were older than 18 years of age, were included. Those who were younger than 18 years of age, had secondary malignancies, had a high body mass index, and were diagnosed with any chronic disease including chronic lung disease, were excluded from the study. Chronic disease was defined as diseases requiring regular medication use for any reason. Normal body mass index was defined as 18-25 Kg/m^2. Demographic data, height, body surface area (BSA), blood parameters (complete blood count, routine biochemistry parameters and tumor markers), DLCO and PFT results before and after treatment were obtained retrospectively. NLR, PLR, neutrophil and lymphocyte values at the beginning of the treatment were recorded. NLR and PLR were calculated with the formula: neutrophil count (/μL)/Lymphocyte count (/μL) and platelet count (10^9/L)/lymphocyte count (/μL). DLCO was determined using the single-breath method and corrected for hemoglobin content and for alveolar volume (DLCO/VA) by using Cosmed Quark PFT. The cut-off for DLCO reduction was taken as >10% in this study.[14]

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25 (IBM, Armonk, USA). In descriptive statistical analyses, categorical data were given as frequency (percentage), numerical data as median (range) or mean (standard deviation). Independent sample t-test was used to compare parametric variables. Spearman correlation analysis were performed to determine relationships between the variables. Multivariate regression analysis was performed to determine independent factors predicting DLCO change. Statistical analysis of this study was made in two-tailed and a $p < 0.05$ was considered statistically significant.

RESULTS

The median age of the patients was 29.5 (17-69) years. Thirty-one (77.5%) of the patients were diagnosed with non-seminomatous TCa, 9 (22.5%) were diagnosed with seminomatous TCa. Demographic and pathological features of the patients are presented in Table I.

Table I: Patients characteristics before treatment.

	Seminoma (n=9)	Non-seminoma (n=31)	Total (n=40)
Age (median)	31 (18-44)	29 (17-69)	29.5(17-69)
Active smoker	3 (33.3%)	13(41.9%)	16 (40%)
Former smoker	1 (11.1%)	4 (12.9%)	5 (12.5%)
Non-smoker	5 (55.6%)	12(38.7%)	17(42.5%)
Unknown	0	2 (6.5%)	2(5%)
Stage			
1	1(11.1%)	12(38.7%)	13 (32.5%)
2	5(55.6%)	8(25.8%)	13 (32.5%)
3	3(33.3%)	11 (35.5%)	14 (35%)
S0	7 (77.8%)	11 (35.5%)	18 (45%)
S1	2 (22.2%)	17 (54.8%)	19 (47.5%)
S2	0	1 (3.2%)	1 (2.5%)
S3	0	2 (6.5%)	2 (5%)
Metastatic site			
Lymph node	6(66.7%)	17(54.8%)	23(57.5%)
Retroperitoneal	4 (44.4%)	14(45.2%)	18(45%)
Mediastinal	2 (22.2%)	7 (22.6%)	9 (22.5%)
Lung	2 (22.2%)	6 (19.3%)	8 (20%)
liver	1 (11.1%)	0	1 (2.5%)
Risk group			
Good	7 (77.8 %)	23 (74.2%)	30(75%)
İntermediate	2(22.2 %)	1 (3.2%)	3 (7.5%)
Poor	-	7 (22.6%)	7 (17.5%)

Table II: Decrease of ≥10% in DLCO *vs.* No decrease or a decrease of ≤10% in DLCO.

	DLCO		
	Decrease of ≥10% n:16	Decrease of <10% n:13	p
NLR, mean ±sd	3.03±1.45	1.68±0.73	0.005
Neutrophil (10^3)	4.70±1.42	4.44±1.53	0.635
Lymphocyte (10^3)	1.74±0.60	2.43±0.92	0.023
Platelet (10^3)	298.75±71.13	270.76±53.14	0.250
PLR	187.72±66.90	124.72±47.99	0.008
B-HCG	1601.05±6090.35	8.58±17.39	0.356
AFP	2695.71±10391.27	74.11±120.62	0.373

Table III: Multivariate analysis of the effect of LDH, PLR, Lymphyocyte and NLR.

	OR (95% CI)	p
LDH	1.083 (1.009-1.163)	0.027
PLR	1.064 (1.006-1.126)	0.030
Lymphyocyte	0.405 (0.012-13.478)	0.613
NLR	1.724 (0.143-20.824)	0.668

The proportion of patients receiving 3 and 4 cycles of BEP was 23 (57.5%) and 14 (35%), respectively. The response assessment was not performed in 2 (5%) patients at the data cut-off time. In 3 (7.5%) patients, the planned number of cycles could not be reached due to side effects. Complete response was obtained in 23 (57.5%), and partial response in 12 (30%) of patients according to response evaluation criteria in solid tumors (RECIST) 1.1 criteria. Two out of the three cases that ended with death were identified to have bleomycin-induced pulmonary toxicity after evaluation of computed tomography imaging of the chest. The other case had severe tumor burden at diagnosis. In all of these patients before chemotherapy, FVC was observed

above 80% of the expected value and FEV1/FVC was above 90% of the expected value.

Considering the DLCO changes before and after treatment, 21 (52.5%) of the patients showed a decrease compared to initial DLCO, while 8 (20%) of the patients had no decrease in DLCO. Of the remaining 11 patients, 3 (7.5%) were unable to undergo control tests due to exitus, while 8 (20%) failed to comply with tests. A decrease of ≥10% in DLCO in 16 patients (40%) and ≥30% in 4 patients (10%) were detected. A statistically significant negative correlation was found between DLCO change and NLR, PLR (r:-0.558, p: 0.002 for NLR; r:-0.462 p: 0.012 for PLR). A statistically significant positive correlation was found between DLCO change and lymphocyte level (r: 0.436, p: 0.018).

The NLR ratio was statistically higher in the group with a decrease of ≥10% in DLCO compared to the group with no decrease or a decrease of ≤10% in DLCO (3.03 ± 1.45 and 1.68±0.73, respectively; p=0.005). In addition, when patients with and without ≥10% decrease in DLCO was compared, the values of PLR (187.72 ± 66.90 and 124.72 ± 47.99, respectively; p=0.008) were significantly higher than those with decrease. Furthermore, lymphocyte levels were found to be statistically significantly lower in the group with a decrease of ≥10% in DLCO, compared to the remaining patients (1.74 ± 0.60 and 2.43 ± 0.92, respectively; p=0.023, Table II).

Multivariate regression analysis showed a statistically significant relationship between LDH and PLR increase and a decrease of ≥10% in DLCO (p=0.027 for LDH; p=0.03 for PLR). Increases in LDH and PLR were found to be independent predictive factors for DLCO decline (Table III).

DISCUSSION

In this study, it was shown that low lymphocyte count, NLR, PLR and LDH values may be predictive for DLCO reduction, while PLR and LDH values also seem to be independently associated with DLCO reduction in patients diagnosed with TCa receiving bleomycin.

The pulmonary toxicity of bleomycin has a mortality rate of around 1–3%, considering that its frequency can reach up to 20%,[2-4] it is apparent that predicting the pulmonary toxicity of bleomycin is critical. DLCO remains an easy method to demonstrate pulmonary toxicity. On the other hand, NLR has been used as a biomarker in many different types of cancer.[15-17] Increased neutrophil levels induce systemic inflammatory response, while low neutrophil levels reduce bleomycin-induced pulmonary toxicity.[11] Additionally, low lymphocyte levels have been associated with high disease severity.[11] In many studies, it has been claimed that combining these two parameters may provide more consistent results.[11,15] In this study, similar to many previous studies, elevation of NLR ratio was found to be significantly associated with DLCO decline; thus, indicating it may be valuable for the evaluation of bleomycin-induced pulmonary toxicity.[11] Low lymphocyte levels were also statistically significantly associated with DLCO decline. As BMI values in the ideal range were among the inclusion criteria of this study, the confounding effects of obesity on this type of inflammation scoring were prevented.[18] Lack of such inclusion criteria in other studies,[19] is an important consideration adding value to the present results.

The PLR is an inflammatory marker, such as NLR. In many studies conducted in patients with cancer, the elevation of PLR was found to be associated with tumor aggressiveness.[19] When the English literature was searched, no direct data were found that would be statistically significant between DLCO and PLR in patients who received bleomycin. In a previous study, no statistically significant correlation was found between PLR and bleomycin-induced pulmonary toxicity in patients with TCa.[11] In this study, it was found a statistically significant relationship between elevation of PLR level and DLCO decline. In addition, it has been shown that PLR is an independent predictive factor for DLCO decline in multivariate analysis. Even though utilising a proxy to evaluate relationships may cause limitations, the authors believe the novel relationship between DLCO and PLR shown in this study is an important initial step for further research on this subject. Unlike previous studies where primary confounding factors were not excluded, this research performed a homogenous evaluation of patients with TCa receiving bleomycin. Even so, it is still possible that the distribution of unidentified risk factors could have influenced results.

There were two patients (5%) who died from bleomycin-induced pulmonary toxicity. This rate was similar to other studies.[2-4] A decrease of ≥10% in DLCO was observed in 16 patients (40%) after bleomycin exposure. When two patients, who died due to bleomycin toxicity, were added to these patients, the frequency of ≥ 10% decreased DLCO was found at a rate of 55%. Although this result showed that DLCO decline was a sensitive method in demonstrating bleomycin toxicity, the specificity of clinically significant DLCO decline was found to be low, similar to other studies.[6,9]

The relatively small number of patients and the inability to obtain a high-resolution computed tomography (HRCT) for the assessment of subclinical DLCO changes may be considered as the primary limitations of this study. In addition, NLR and PLR values may vary due to infection, bleeding, and steroid-derived drug use. Since this study was retrospective, these interactions could not be fully evaluated. Further studies are needed to demonstrate these relationships more comprehensively.

CONCLUSION

It has been shown that PLR could be used as independent predictive biomarkers for DLCO decline, which is used to identify bleomycin-induced pulmonary toxicity. In the light of this data, it may be recommended that DLCO follow-ups be done more frequently in patients with high PLR values.

ETHICAL APPROVAL:

This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was

approved by the local Institutional Review Board (No. January 2021/113).

PATIENTS' CONSENT:
Since it was designed as a retrospective study, the data were collected from the hospital archive following the approval of the Ethics Committee.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
SK, IK, CO, ED, OA, OBCO: Conceived the study design, involved in data collection, performed the statistical analysis, interpreted the data, and prepared the manuscript draft.
All the authors critically reviewed the final version of the manuscript and approved the final version to be published.

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