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Original Article

Internal Medicine Section

Predictors of Response to Chemotherapy in Patients with Advanced Non-small Cell Lung Cancer: A Prospective Cohort Study

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ABSTRACT

Introduction: Lung cancer carries the highest cancer-related mortality rates worldwide. Despite all recent advances, the mortality from lung cancer is still rising. A better understanding of the risk factors may help us predict responses to chemotherapy for better management.

Aim: To evaluate predictors of response to chemotherapy in advanced Non-Small Cell Lung Cancer (NSCLC) patients.

Materials and Methods: This was a prospective cohort study conducted in the Department of Pulmonary Medicine at Government Medical College and Hospital, Chandigarh, India. A total of 60 confirmed cases of advanced (stage IIIB and IV) NSCLC patients were enrolled consecutively for a duration of two years. Baseline clinical parameters, routine blood tests, spirometry, exercise capacity using the 6 Minute Walk Test Distance (6MWTD), and Computed Tomography (CT)-based tumour size were recorded. Certain pre-defined patient, disease, and therapy-related factors (age, gender, dyspnoea, baseline blood tests, tumour size, histology, etc.) were evaluated for their possible role as predictors of treatment response in advanced NSCLC patients. A positive response was defined if the response to chemotherapy was Complete Response (CR) or Partial Response (PR), and a negative response if the response was Progressive Disease (PD) or Stable Disease (SD) as per revised RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria. Variables between the two groups were compared using the Mann-Whitney U test and Chi-square test. To find out the factors that may predict response to treatment, univariate and multivariate logistic regression analysis were used.

Results: Out of a total of 60 confirmed cases of NSCLC patients, only 40 patients were able to complete the four cycles of chemotherapy. The mean age of the patients was 58.5±9.6 years. There were a total of 35 males (87.5%) and five females (12.5%) in the study. Out of 40 patients, 27 (67.5%) had squamous cell carcinoma and 13 (32.5%) had adenocarcinoma. On univariate analysis, Neutrophil-Lymphocyte Ratio (NLR) had a statistically significant association with tumour response ($p<0.001$). On multivariate analysis, advanced age ($p=0.05$) and high (>3.81) NLR ($p=0.002$) were found as independent predictors of poor response to chemotherapy.

Conclusion: Pre-treatment high NLR and advanced age are significant factors for a poor response to chemotherapy treatment in advanced NSCLC patients.

Keywords: Cancer related mortality, Computed tomography, Squamous cell carcinoma

INTRODUCTION

Lung cancer is the most common malignancy worldwide and carries the highest cancer-related mortality rates [1]. Despite recent advances in the management of lung cancer, mortality continues to rise in middle and low-income countries [2]. More than 9.3 percent of deaths in India are directly related to lung cancer [3]. The histology of more than 80 percent of all primary lung cancers is of the NSCLC type [4]. Despite numerous recent advances in terms of new diagnostic methods and therapeutic interventions, the outcomes of lung cancer have remained below average. Approximately two-thirds of NSCLC patients present in the advanced stages (Stage III and IV) of the disease at the time of diagnosis [5]. The overall five-year survival rate for advanced NSCLC patients is 12 to 16 percent, which is two to three times lower (5 percent) in developing countries [6].

With the advent of new chemotherapeutic regimens, including targeted therapies, the response rate and survival in these patients have shown improvement. However, chemotherapy with or without radiotherapy is the only treatment modality available to patients who are not eligible for targeted therapy. Previous studies have reported variable responses to chemotherapy among different patients, suggesting that the cancer may display different biological behaviour and natural history in different population groups [7-9]. Previous studies have shown that higher age, smoking status, high baseline Platelet-To-Lymphocyte Ratio (PLR), high NLR, Lactate Dehydrogenase (LDH), uric acid, hypercalcaemia, tumour histology, clinical stage IV, and malignant pleural effusion are associated with poor prognosis and shorter Overall Survival (OS) [10-15]. Most of these results were generated from western populations, and evidence is scarce on the predictors of response to chemotherapy from India [9-15]. Hence, the authors conducted a study to evaluate predictors of response to chemotherapy in advanced NSCLC cancer patients in a tertiary care centre in North India.

MATERIALS AND METHODS

A prospective cohort study was conducted in the Department of Pulmonary Medicine in collaboration with the Department of Radiotherapy and Oncology at Government Medical College and Hospital, Chandigarh, India, from July 2016 to August 2018. This study was approved by the institutional medical sciences and ethical committee (No. 6915/GM/17).

A total of 60 confirmed cases of advanced NSCLC patients (clinical stage IIIB and IV as per 7th Tumor, Node, Metastasis (TNM) staging) [16] were consecutively enrolled.

Inclusion criteria: Histopathology/cytopathology-proven NSCLC cases (clinical stage IIIB and IV as per seventh TNM staging) [16] and willing to undergo palliative chemotherapy with or without radiotherapy and with a performance status of 0-2 (as per Eastern Cooperative Oncology Group (ECOG) [17].

Exclusion criteria: Patients ineligible for chemotherapy due to haemodynamic instability, those positive for Epidermal Growth Factor Receptor (EGFR) mutations and the ones not willing to undergo treatment were excluded from the study.

Procedure

Total of 60 patients were included in the study. They underwent detailed demographic information collection, including history and clinical examination, symptoms, smoking history, and co-morbidities. All patients underwent routine spirometry and exercise capacity assessment using 6MWTD [18]. Based on revised RECIST 1.1, baseline tumour burden was calculated by CT-based tumour size measurement [19]. Tumour-related factors like baseline tumour size, clinical stage, histology, and presence of malignant pleural effusion were recorded. Routine blood investigations, like Haemoglobin (Hb), NLR, creatinine, uric acid, LDH, and calcium, were also recorded. All patients received four cycles of palliative chemotherapy with or without radiotherapy as per standard guidelines after baseline evaluation.

Certain pre-defined (patient, disease, and therapy-related) factors were analysed for their role as predictors of treatment response (based on revised RECIST criteria 1.1) [19]. The evaluation of target lesions' response was done in terms of CR, PR, PD, SD. For statistical analysis, patients were divided into two groups: the "response" group if the response to treatment was CR or PR, and the "no response" group if the response to treatment was PD or SD.

STATISTICAL ANALYSIS

All baseline numerical variables were summarised using mean±standard deviation or median (Range) depending on the distribution. Categorical data were summarised as frequency (percentage). Continuous variables between two groups were compared using the Mann-Whitney U test, and categorical variables were compared using the Chi-square test. Univariate and multivariate logistic regression analyses were conducted to identify the factors that predict the response to treatment. In all statistical analyses, a p-value of ≤0.05 was considered significant. All analyses were conducted using Statistical Package for Social Sciences (SPSS) (IBM SPSS Statistics 21.0; Armonk, NY, USA).

RESULTS

Out of a total of 60 confirmed cases of NSCLC patients, only 40 were able to complete the four cycles of chemotherapy. The remaining 12 died, and eight were lost to follow-up before completing treatment. The mean age of the patients was 58.5±9.6 years (range 40-76 years). There were a total of 35 males (87.5%) and five females (12.5%) in the study, resulting in a male to female ratio of 7:1. Dyspnoea was the most common presenting symptom, observed in 35 patients (87.5%), followed by cough and fever, seen in 33 (82.5%) and 18 (45%) patients, respectively [Table/Fig-1].

Out of the 40 NSCLC cases, 27 (67.5%) had squamous cell carcinoma, and 13 (32.5%) had adenocarcinoma based on histopathology. The mean serum NLR in the patients was 3.9±1.45 [Table/Fig-2]. A significant difference in the NLR between patients with response and non-response to chemotherapy was observed (p-value <0.001), as shown in [Table/Fig-3]. Receiver Operating Characteristics (ROC) curve analysis was also conducted, revealing that a NLR cut-off of ≥3.81 had reasonable sensitivity (93.8%) and specificity (83.3%).

The mean baseline FEV_1 was higher in patients who showed treatment response than in patients with no response (mean FEV_1 in the response group: 74.9±18.7% vs non-response group: 68.3±13.9%); however, the difference was not statistically significant (p-value=0.28) [Table/Fig-3].

Variables	Characteristics	N=40 n (%)
Age (years)	(mean±SD)	58.5±9.6
BMI (kg/m²)	(mean±SD)	21±2.3
Gender	Male	35 (87.5)
	Female	5 (12.5)
Symptoms	Dyspnoea	35 (87.5)
	Cough	33 (82.5)
	Significant weight loss	26 (65)
	Fever	18 (45)
	Haemoptysis	8 (20)
	Hoarseness	5 (12.5)
Tobacco smoking	Ever smokers (>30 pack years)	31 (77.5)
Comorbidities	Previous history of pulmonary tuberculosis	10 (25)
	Hypertension	5 (12.5)
	Diabetes	4 (10)

[Table/Fig-1]: Baseline demographic profile of patients.
SD: Standard deviation; BMI: Body mass index; kg: Kilogram; m: Meter

Investigations	Variables	Mean±SD
Blood investigations	Haemoglobin (gm/dL)	10.5±2.2
	Platelet count (10^5/µL)	2.74±1.14
	Serum NLR	3.9±1.45
	Serum creatinine (mg/dL)	1.02±0.35
	Serum calcium (mg/dL)	8.9±1.6
	Serum uric acid (mg/dL)	5.6±2.6
	Serum LDH (IU/L)	638.6±26
	Serum albumin (gm/dL)	3.4±0.6
Six Minute Walk Test Distance (6MWTD)	6MWTD (meter)	312.3±92.2
Spirometry	FEV_1 (%)	72.7±17.1
Tumour characteristics	Tumour size (cm)	9.0±3.8
	Squamous cell carcinoma n (%)	27 (67.5)
	Adenocarcinoma n (%)	13 (32.5)
	Malignant effusion n (%)	15 (37.5)
Tumour stage	Stage IV n (%)	24 (60)
	Stage III B n (%)	13 (32.5)
	Stage III A n (%)	3 (7.5)

[Table/Fig-2]: Baseline investigations and tumour characteristics.
LDH: Lactate dehydrogenase; FEV1: Forced expiratory volume in the first second; NLR: Neutrophil-lymphocyte ratio

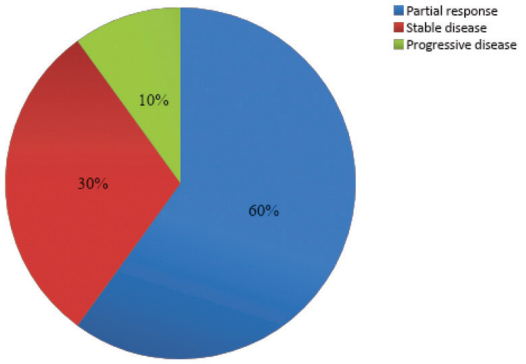
In the study, a total of 24 patients (60%) showed a favourable treatment response (PR), 12 (30%) showed SD, and four (10%) showed PD [Table/Fig-4]. Baseline NLR exhibited a significant association with tumour response (p=<0.001) in univariate logistic regression analysis. In multivariate regression using the significant parameters, age (OR: 0.88; 95% CI 0.78-1.01; p≤0.05) and NLR (OR: 0.08; 95% CI: 0.016-0.41; p=0.002) were found as the only independent predictors that predicted a poor response to treatment [Table/Fig-5].

DISCUSSION

The present study analysed 40 confirmed cases of advanced NSCLC to evaluate factors that may predict outcomes in lung cancer patients after four cycles of chemotherapy. In the study, a total of 24 patients (60%) showed a favourable treatment response (partial/total response). Advanced age and high NLR were found as independent factors predicting response to four cycles of chemotherapy.

S. No.	Variables	Response group	Non response group	p-value
1	**Age (in years)**	56.8±9.7	61±9.2	**0.17€**
2	**BMI (kg/m²)**	23±2.5	22.3±2.7	0.39*
3	**Smoking (pack year)**	58.3±22.8	76.7±31.1	**0.06***
4	**Haemoglobin (gm/dL)**	10.5±2	10.7±2.4	0.73*
5	**Platelet count (10^5/µL)**	2.7±1.2	2.7±0.9	0.98*
6	**Creatinine (mg/dL)**	1.03±0.38	1±0.28	0.74*
7	**NLR**	3.03±0.9	5.23±0.97	**0.001***
8	**Uric acid (mg/dL)**	5.8±3.2	5.2±1.2	0.53*
9	**Calcium (mg/dL)**	9.2±1.5	8.4±1.6	**0.15***
10	**Albumin (gm/dL)**	3.4±0.6	3.3±0.5	0.47*
11	**LDH (IU/L)**	669±308.8	579±186.7	0.30*
12	**Baseline FEV_1 (% predicted)**	74.9±18.7	68.3±13.9	0.28*
13	**Baseline 6MWTD (meters)**	317±101	304.8±80.6	0.69*

[Table/Fig-3]: Distribution of baseline variables in advanced NSCLC patients among 2 treatment outcome groups.
BMI: Body mass index; LDH: Lactate dehydrogenase; NLR: Neutrophil to lymphocyte ratio; FEV_1: Forced expiratory volume in the first second; 6MWTD: Six minute walk test distance; *=Mann-Whitney U test; €=Chi-square test



[Table/Fig-4]: Distribution of treatment response in NSCLC patients.

Variable	Univariate analysis OR (95% CI)	p-value	Multivariate analysis OR (95% CI)	p-value
Age (years)	**0.95 (0.89-1.03)**	**0.17**	**0.88 (0.78-1.01)**	**0.05**
Gender (Female)	1.1 (0.14-7.14)	**0.1**		
BMI	1.12 (0.90-1.42)	0.38		
Weight loss	1.2 (0.32-4.49)	0.78		
H/O Smoking	0.69 (0.14-3.3)	0.64		
Haemoglobin	0.95 (0.70-1.28)	0.72		
Uric acid	1.11 (0.81-1.49)	0.53		
Calcium	1.35 (0.89-2.08)	**0.15**		
NLR	**0.13 (0.042-0.43)**	**0.001**	**0.08 (0.016-0.41)**	**0.002**
Albumin	1.51 (0.50-4.54)	0.46		
Lactate dehydrogenase	1.01 (1-1.01)	0.30		
Creatinine	1.38 (0.21-1.75)	0.73		
Platelet count	0.99 (0.57-1.75)	0.98		
H/O Pleural effusion	0.64 (0.17-2.36)	0.50		
Tumour stage	0.85 (0.31-2.38)	0.76		
Baseline tumour size	1.05 (0.87-1.25)	0.62		
Baseline FEV1 (in % of predicted)	1.03 (0.98-1.07)	0.28		
COPD	1.2 (0.29-4.9)	0.80		
Baseline 6MWTD	1.01 (0.99-1.01)	0.68		
Baseline dyspnoea	0.89 (0.30-2.63)	0.82		

[Table/Fig-5]: Univariate and multivariable analysis of predictors of response in NSCLC patients after 4 cycles of chemotherapy.
BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CI: Confidence interval; FEV1: Forced expiratory volume in the first second; 6MWTD: Six minute walk test distance; NLR: Neutrophil to lymphocyte ratio; OR: Odds ratio

Out of the 40 confirmed NSCLC cases, 24 (60%) were diagnosed in stage IV (7th TNM), and there was no statistically significant difference in the treatment response seen among different tumour stages (p>0.05). In contrast, previous studies have indicated that higher tumour stage is associated with a worse prognosis in advanced lung cancer patients treated with chemotherapy [13,15,16]. This variability might be due to the small sample size of the present study as well as differences in the study population, chemotherapy regimens, and staging criteria used in these studies.

In the multivariate model, NLR was found to be a statistically significant independent prognostic factor for a poor response to chemotherapy (OR 0.08 and 95% CI 0.016-0.41; p-value=0.002) in the present study. The peripheral NLR represents the burden of the ongoing inflammatory process in the tumour microenvironment. Neutrophils release active chemicals that assist tumour cells in migrating through the extracellular matrix and vasculature to distant metastatic sites [20]. However, the exact mechanism by which the NLR impacts prognosis still remains unclear.

A retrospective study conducted in 401 patients with advanced NSCLC treated with first-line chemotherapy or targeted therapy showed that factors like ECOG-PS, tumour stage, histology, EGFR status, and NLR (HR 1.74, 95% CI 1.26-2.41; <0.001) were significant predictors of OS [21]. In a recent meta-analysis of 19 studies comprising 7,283 patients with lung cancers, it was found that high NLR (p<0.00001) and high PLR (p=0.01) were significantly associated with poorer prognosis and worse OS [22]. High NLR and PLR were significantly associated with deeper tumour invasion (p=0.006), extensive lymph node metastasis (p=0.01), poor differentiation (p=0.0002), and vascular invasion (p=0.002). The calculated NLR cut-off value for differentiating between treatment response and failure was 5 [22]. However, in the present study, the ROC curve for the NLR cut-off value in detecting a response to treatment in advanced NSCLC was 3.81.

High post-chemotherapy NLR was correlated with a higher risk of mortality (HR=1.13, 95% CI 1.06-1.21; p<0.001) in the study by Lee Y et al., [23]. However, high pre-chemotherapy NLR (HR=1.807, p=0.018 for PFS, HR=1.761, p=0.020 for OS) and multiple metastasis (HR=2.118, p=0.008 for PFS, HR=2.753, p<0.001 for OS) were found to be poor prognostic markers for Progression-Free Survival (PFS) and OS by a study by Yao Y et al., [24]. Previous meta-analyses also confirmed that a high NLR was a predictor of poorer OS and shorter PFS in patients with advanced lung cancer [14,22,25,26]. The majority of these previous studies are retrospective and derived from Western populations. Being retrospective, they are susceptible to selection biases. Moreover, the presence of biological heterogeneity might have affected the interpretation of the results of the meta-analyses. The value of NLR can be influenced by the effect of various immuno-modulatory drugs like steroids, as well as concurrent infections. Particular inflammatory markers of infection, like C-Reactive Protein and procalcitonin, might be useful to exclude infections in such situations [22].

Tumour histology has also been evaluated for its effect on the treatment response in NSCLC in previous studies, where non-adenocarcinoma tumour histology was associated with worse survival outcomes [27-29]. The present study didn't find any significant association between tumour histopathology and response to chemotherapy. Few previously published studies also did not find any significant association between tumour histology and response to chemotherapy [15,30,31]. This variation, though not fully understood, might be due to the small sample size in the present study.

Advanced age (>60 years) was associated with a poor treatment response to chemotherapy in the present study (OR 0.88, 95% CI

0.78-1.01; p=0.05). However, in a previous study performed by Albain KS et al., age >70 years was associated with improved outcomes in patients with advanced NSCLC treated with chemotherapy [32]. An increase in age is usually associated with a decrease in functional capacity and an increase in co-morbidities that are likely to affect the treatment outcome.

Other baseline patient characteristics like smoking history, weight loss >5% of body weight, co-morbidity, lower (<18.5) BMI, ECOG >II, tumour stage IV, >2 metastatic sites have been shown to negatively impact the overall response and survival in NSCLC patients in other studies [10,12,15]. However, the authors did not find these baseline characteristics statistically significant in the present study.

The previous study results showed that low serum albumin levels were associated with a poor prognosis and OS [33,34]. However, the present study revealed no statistically significant association with the treatment response (p=0.66). Apart from albumin, a higher concentration of serum uric acid has also been found to be associated with a good prognosis and increased overall patient survival in a few studies [27,35]. Nevertheless, the present study didn't show any statistically significant difference between the uric acid level and the response to chemotherapy. Serum uric acid levels are influenced by various other factors, including food habits (increased purine-rich diets) and alcohol consumption.

In this study, there was a statistically significant correlation between a higher pre-treatment NLR and a poor response to conventional chemotherapy in EGFR mutation-negative advanced NSCLC patients. The findings suggest that NLR could be a potential cost-effective and easily available biomarker for chemotherapy response and prognosis.

Limitation(s)

The present study also had some limitations, including a short study duration, a small sample size, and the absence of enrolled EGFR mutation patients, which might have affected the results. Increasing the sample size in future prospective studies might help us validate the results and predict OS.

CONCLUSION(S)

Factors like higher NLR and advanced age (>60 years) are significant predictors of poor response to conventional chemotherapy in EGFR mutation-negative advanced NSCLC patients. India is a high-burden country for lung cancer. Knowledge of such predictors of response before initiating treatment may help us categorise patients for better management and guide the tailoring of therapy.

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- Manual Googling: Jan 01, 2024
- iThenticate Software: Jan 04, 2024 (13%)

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- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
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