Inflammatory prognostic biomarkers in advanced non-small cell lung cancer

Dear Editor,

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer. In spite of the progress achieved in treatments, patients with advanced disease still have a poor prognosis. Prognostic evaluation in cancer is a challenging process. Features such as age, gender, histopathology and stage are known prognostic factors, but are not enough to explain the global prognosis.[1] Therefore, new prognostic markers are needed. The use of biological markers easily collected through a simple method like a peripheral blood sample is appealing. The ideal biomarker should have a long half-life, be measured precisely by an inexpensive and simple test, and be sensitive to change so that it can be followed over time. C-reactive protein (CRP) and neutrophil-to-lymphocyte ratio (NLR) meet these criteria and elevated levels of these biomarkers have been linked to poor prognosis in several cancers.[2]

The aim of this work was to evaluate the relationship between CRP and NLR values at the time of diagnosis and the overall survival (OS) in patients with NSCLC at stages IIIB and IV.

We performed a retrospective study that included patients diagnosed with NSCLC at stages IIIB and IV (based on the tumor-node-metastasis classification, 7th edition) between January 2012 and March 2016, who were treated with palliative systemic therapy. Patients with clinical evidence of infection at the time of diagnosis were excluded since infection is a non-cancer inflammatory marker-modifying factor. CRP and NLR values at the time of diagnosis and other clinical variables were retrieved from patients' medical records. The NLR ratio was calculated dividing the absolute neutrophil count by the absolute lymphocyte count. In accordance to previous studies,[3,4] a cut-off value of 3.5 was evaluated as a potential prognostic biomarker. The cut-off value of CRP varies among different studies, but a systematic review verified that 10 mg/L was the most frequently selected.[2] Accordingly, we adopted this value as cut-off.

Kaplan–Meier analysis with log-rank test was performed to calculate median OS. Univariate and multivariate analyses for OS were performed using the Cox proportional hazards model and was expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS® for Windows® (version 24.0, Chicago, Illinois).

Patient characteristics are shown in Table 1. From a total of 569 patients diagnosed with NSCLC, 318 fulfilled the required criteria, 262 (82.4%) of which at stage IV. Most patients had increased values of CRP (60.1%) or NLR (56.6%) at the time of diagnosis. Male gender, loss of 5% or more of body weight before diagnosis, an Eastern Cooperative Oncology Group (ECOG) ≥ 2, NRL > 3.5 and CRP > 10 mg/L were significantly associated with worse OS (Table 2). NLR and CRP were independent prognostic factors for OS when adjusted by the other clinical factors.

Table 1 Clinicopathological features at diagnosis.

Characteristics at diagnosis		Number of patients (%)[a]
Age (years)		70 ± 12
Gender	Female	76 (23.9)
	Male	242 (76.1)
Performance status	ECOG 0	41 (12.9)
	ECOG 1	193 (60.7)
	ECOG 2	58 (18.2)
	ECOG 3	19 (6)
	ECOG 4	7 (2.2)
Weight loss	<5%	122 (38.4)
	5–10%	124 (39)
	>10%	72 (22.6)
Smoking status	Never smoker	78 (24.5)
	Ex-smoker	118 (37.1)
	Current smoker	122 (38.4)
Histopathology	Adenocarcinoma	215 (67.6)
	Squamous cell carcinoma	67 (21.1)
	Others	36 (11.3)
TNM staging	IIIB	56 (17.6)
	IV	262 (82.4)
NLR	≤3.5	138 (43.4)
	>3.5	180 (56.6)
CRP	≤10 mg/L	127 (39.9)
	>10 mg/L	191 (60.1)

[a] Age is displayed as mean ± standard deviation.
CRP – C-reactive protein; ECOG – Eastern Cooperative Oncology Group; NLR – neutrophil–lymphocyte ratio; TNM – tumor-node-metastasis.

Patients with NLR > 3.5 had increased risk of death (HR 1.350; 95% CI 1.036–1.760; $p = 0.026$). The same was verified with CRP, with values >10 mg/L predicting worse survival (HR 1.462; 95% CI 1.113–1.920; $p = 0.006$). Among the other clinical variables, ECOG ≥ 2 and male gender also independently predicted worse survival. The two biomarkers were then combined to obtain four subgroups: group A with decreased values of both markers (67 patients), group B with CRP $\leq$ 10 mg/L and NLR > 3.5 (60 patients), group C with CRP > 10 mg/L and NLR $\leq$ 3.5 (71 patients), and group D with both markers increased (120 patients). Patients from group A had a median survival of 24 months, significantly higher than those with at least one increased biomarker ($p < 0.001$). Patients from groups B, C and D had similar median survival times (5, 7 and 5 months, respectively, $p > 0.05$) (Fig. 1).

Several studies have demonstrated a relationship between CRP and NLR values and survival in cancer patients.[2,3] It has been reported that inflammation could facilitate cancer development and is associated with a worse outcome.[5] Systemic inflammation can be accessed by NLR and CRP blood levels, two minimally invasive and inexpensive biomarkers.[2]

We observed that the presence of NRL > 3.5 or CRP > 10 mg/L was independently associated with shorter OS. We found no cumulative effect on OS when both biomarkers are increased. Besides, each of these markers increases the hazard of death in the same magnitude. Our results suggest that it is the presence of inflam-

Table 2 Prognostic factors for overall survival estimated by univariate and multivariate Cox regression analyses.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Male gender	1.553	1.146–2.105	**0.003**	1.408	1.032–1.921	**0.031**
Ever smoker	1.150	0.866–1.528	0.335			
ECOG ≥ 2	1.897	1.451–2.480	**<0.001**	1.711	1.289–2.272	**<0.001**
Weight loss ≥ 5%	1.348	1.043–1.741	**0.022**			
NSCLC other than adenocarcinoma	1.211	0.934–1.571	0.148			
NLR > 3.5	1.694	1.315–2.183	**<0.001**	1.350	1.036–1.760	**0.026**
CRP > 10 mg/L	1.766	1.361–2.291	**<0.001**	1.462	1.113–1.920	**0.006**

CRP – C-reactive protein; ECOG – Eastern Cooperative Oncology Group; HR – hazard ratio; NLR – neutrophil–lymphocyte ratio; NSCLC – non-small cell lung cancer.
Statistically significant values are in bold.

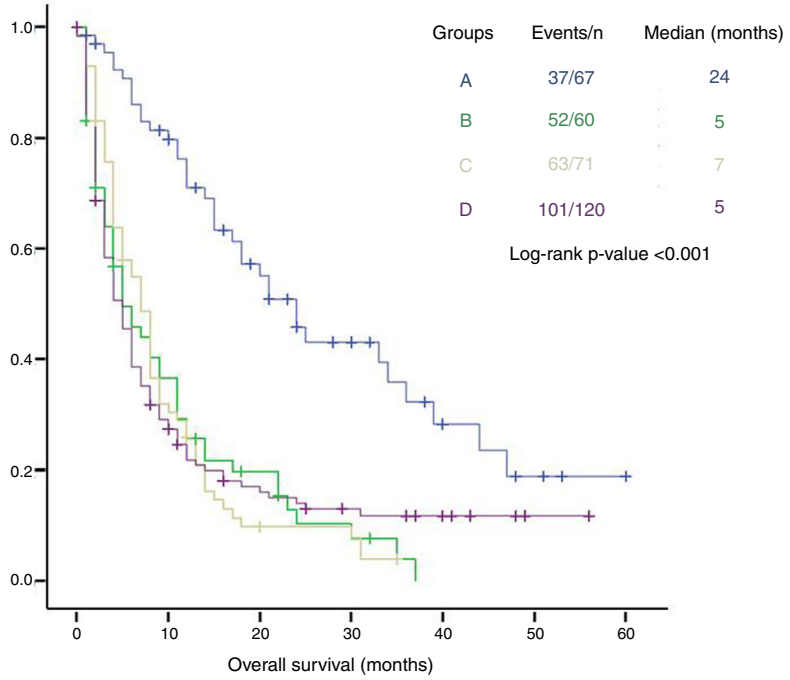

Figure 1 Overall survival according to biomarkers groups. (A) CRP ≤ 10 mg/L and NRL ≤ 3.5. (B) CRP ≤ 10 mg/L and NLR > 3.5. (C) CRP > 10 mg/L and NRL ≤ 3.5. (D) CRP > 10 mg/L and NRL > 3.5.

mation in lung cancer that is associated with worse prognosis, rather than the marker chosen for its evaluation. Cancer-related inflammation affects many aspects of cancer including proliferation and survival of tumor cells, angiogenesis, metastization and tumor response to therapy.[6] Previous studies have also evaluated this association between increased inflammation and worse survival in lung cancer. As in ours, the majority have identified increased values of NLR or CRP to be associated with worse OS.[1,2,7]

These results highlight the importance of routinely assessing the presence of systemic inflammation as a part of the global approach of patients with lung cancer.

We recognize some limitations in our study. First, it is a retrospective and single center study, with inherent selection bias. Second, although patients with evidence of infection were excluded, we cannot ensure that other non-cancer CRP and NLR modifying factors were present. Third, mutational status and treatment regimens were not reported and may have influenced results.

In conclusion, the results of this study demonstrated that CRP and NLR are independent prognostic factors for advanced stage NSCLC patients, but additional studies are necessary to assess if long term monitoring of these biomarkers will be helpful in outcomes evaluation.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

Dr. Barroso reports personal fees from AstraZeneca, Boehringer Ingelheim, Lda, Eli Lilly and Company, Pierre Fabre Portugal, Roche Farmacêutica Química, Lda, Merck and Bristol-Myers Squibb, outside the submitted work. The other authors have no conflicts of interest to declare.

Acknowledgements

None.

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https://doi.org/10.1016/j.pulmoe.2019.02.007
2531-0437/

Immunotherapy in Allergic Asthma – 5 year analysis: Is it a curative approach?

Dear Editor,

Asthma is a common, chronic and heterogeneous disease; it affects people of all ages and there has been a recent increase in its prevalence and severity. It may be mild, barely noticed by the patient, or it may range all the way to very severe disease, causing constant symptoms that greatly affect the quality life of the patient. The long-term goals of asthma management are to achieve good symptom control and minimize future risk of exacerbation, fixed air flow limitation and treatment of side effects.[1] The patient own goals regarding their asthma and its treatment should also be identified. During the last decade several new drugs addressing asthma have been developed and approved.

The immune system is a complex interactive network with the capacity of protecting the host from a number of pathogens while maintaining a state of tolerance to self and innocuous exogenous antigens. Allergy is one of the immune tolerance-related diseases that arises as a direct consequence of a dysregulated immune response.

Currently, allergen-specific immunotherapy (allergen-SIT) remains the single curative approach to allergic diseases with the potential to modify its course.[2] It is proven to be the only therapy that alters the natural history of allergic disease, prevents progression, prevents the development of new sensitizations and may even prevent the development of asthma in patients with allergic rhinitis.[3] It consists of administering gradually increasing doses of a specific allergenic extract to an allergic subject (with specific documented IgE), at an effective dose, in order to decrease the symptoms associated with subsequent exposure to the causative allergen.[3] Multiple mechanisms are involved in the suppression and/or control of allergic inflammation.[4] The aim of allergen-SIT is to induce the peripheral T cell tolerance, modulate the thresholds for mast cell and basophil activation and decrease IgE-mediated histamine release.[4] Peripheral T cell tolerance is characterized by the generation of allergen-specific T-regulatory cells (Treg) that are able to produce anti-inflammatory cytokines such as IL-10 and TGF-b.[5] Treg cells not only diminish Th2 immune responses, but also target other cell types such as mast cells, basophils, eosinophils, allergen-specific-IgE and are capable of inducing IgG4 and IgA production.[6]

A review of Abramson et al., which included eighty-eight trials, showed a significant reduction in asthma symptoms, reduction in use of medications and improvement in bronchial hyper-reactivity following immunotherapy.[7] According to the Global Initiative for Asthma (GINA) 2017, for patients with allergic rhinitis and sensitization to house dust mite, with exacerbations despite low-high dose of ICS, we must consider adding sublingual allergen immunotherapy