Editorial

Inflammatory status and prognosis of locally advanced non-small cell lung cancer

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Parameters determined in blood tests are useful for physicians in diagnosis and of clinical management in different medical settings. Among the many different blood test parameters, the neutrophil-lymphocyte ratio (NLR), defined as the ratio between the absolute neutrophil count and the absolute lymphocyte count, is becoming to attract increasing attention. NLR is a parameter easy to determine and low cost that is being associated with prognosis in various pathologies (1). Recently, an interesting article reported the prognosis power of NLR for overall survival (OS) in non-small cell lung cancer (NSCLC) patients diagnosed and treated in locally advanced stage (stages IIIA and IIIB) (2). In this retrospective study NLR was measured in more than 250 patients before chemotherapy, radiotherapy and/or radical surgery, and they were followed-up for a median time of 4.7 years. Authors divided patients in groups using a cut-off value of 5 for NLR, according to other cancer studies. They found a statistically significant difference in OS between NLR <5 patients (29 months) and NLR ≥5 patients (11 months). Authors conclude that NLR, at the time of diagnosis, is a good biomarker for accurate prognosis and should be used in all advanced stage NSCLC patients. Their interpretation is that NLR depicts the immune balance in the cancer patient; an elevation of this marker would represent an "inflammatory status" key to tumor progression pathways. An unresolved question after reading the article is whether this parameter is powerful enough to measure the full immune response in all stages of tumor disease.

First mentions of NLR in medical journals date from 80's and interestingly, lung cancer was the disease under study. Nakahara *et al.* (3) included this parameter as a nonspecific immunological variable within a combined variable called biological status; lower NRL values determined lower scores for this variable. Results showed that patients with higher score had worse long-term prognosis. NRL has been successfully used as prognosis biomarker in other lung diseases such as community-acquired pneumonia (4) and sarcoidosis (5).

Several studies have established the usefulness of this variable as prognosis marker in different histological subtypes and in different stages of lung cancer: in early stage surgically resected NSCLC (6), in advanced stage NSCLC (7), or in small cell lung cancer (SCLC) (8). The work published by Scilla *et al.* (2) demonstrates the strength of this parameter in locally advanced (stage III) NSCL patients, commonly excluded from the majority of clinical studies. Moreover, a meta-analysis of 3,656 patients from 14 studies concluded that pretreatment NLR with a cut-off value of 5 was a good prognosis marker for both OS and progression-free survival in NSCLC (9).

Explanation of the good quality of this parameter is a pending issue not clarified by Scilla *et al.* The increase of NLR can be caused by an increase of neutrophils, a reduction of lymphocytes, or by both situations acting simultaneously. Hence, one possible explanation could be

a direct effect of neutrophils in the oncogenesis process. Neutrophil functions such as cytokine production, protease generation or reactive oxygen species release are involved in extracellular matrix proteolysis, which facilitates metastasis spread (10). Furthermore, neutrophil activation in the lung tissue is a powerful inhibitor of DNA repair mechanisms through myeloperoxidase production, which enhances the accumulation of mutations (11).

Besides, activation of neutrophils associates with the formation of neutrophil extracellular traps (NETs) and several oncogenic processes: adhesion at distant organ sites, migration/invasion ability, enhanced tumor growth and angiogenesis (12). Another possible explanation could be that circulating neutrophil levels are only a marker of global inflammation: the increase of neutrophils would be the result of the increase of inflammatory cytokines (IL-1β, IL-6, IL-23, TNF-α) present in peripheral blood, as a result of nuclear transcription factors NF-κB and STAT-3 activation. Although according to classic theory the induction of NF-κB and STAT-3 could be triggered by mutations in tumor cells, this induction is now believed to be caused by inflammatory activity of peritumoral immune cells in an autocrine/paracrine way (10,13).

Peripheral lymphopenia is another factor implicated in NRL increase. In this sense, lymphopenia was reported as a confirmatory marker of malignancy in the follow-up of solitary lung nodules patients (14). However, the mechanisms of lymphopenia in cancer patients remain unclear and are probably multifactorial (15). Maybe the most studied mechanism involved is overexpression of the cytokine TGF-β (16). This cytokine, directly or through inhibition of the cytokine IL-2, blocks T-cell proliferation and alters cytotoxic T-lymphocyte (CTL) differentiation, thereby producing both quantitative and qualitative immunosuppression (17). Interestingly, the main adaptive antitumoral immune mechanism involved in cancer protection is the killing of tumor cells by CD8+ CTLs (18).

NLR could be associated with the level of lymphocytes found within tumors, known as tumor-infiltrating-lymphocytes (TILs). The association of NLR with the severity of tumor infiltration by TILs has been studied in NSCLC. High values of NLR are related to higher concentration of peritumoral TILs, and both parameters are associated with worse prognosis in NSCLC patients (19).

Some treatments might have an indirect effect in the balance between neutrophils and lymphocytes thereby modifying NLR. Nonsteroidal anti-inflammatory drugs (NSAIDs) can block neutrophil recruitment through different molecular pathways and they have the potential to alter the balance between neutrophils and lymphocytes. Moreover, the use of NSAIDs during and after surgery could modify tumor microenvironment and also reduce migration and invasion of circulating malignant cells. A retrospective study analyzing NSAID usage during surgery in NSCLC, showed that patients with a NLR before treatment >5 had lower OS, but this association was independent of NSAIDs intake (20). Therefore, current evidence does not justify NSAIDs usage in lung cancer.

Regulation of lymphopenia could also have an effect on the outcome in neoplastic diseases. Stimulation of lymphocyte precursors the production might have an effect in certain types of tumors. The cytokine interleukin-7 promotes lymphocyte development in the thymus and maintains survival of naive and memory T cell in the periphery. Therefore, the release of this cytokine could improve cancer-associated lymphopenia. Studies with recombinant IL-7 (rhIL-7) in animal models have shown that treatment with this cytokine can improve lymphopenia and reduce tumor growth in several tumor types (21).

In addition to the role of NLR at the time of diagnosis as a prognosis marker in cancer, its role during the course of the disease remains to be studied. Especially intriguing is its putative role in the follow-up of patients treated with biological drugs such as the checkpoint block inhibitors anti-PD-1 and anti-PD-1L. B7-H1 (PD-1L) is a highly expressed molecule in many human cancers and is one of the most important immune escape mechanisms through the induction of apoptotic death by interaction with its ligand PD-1 on activated tumor antigen-specific human T cells (22). Besides this effect, the PD-1/PD-1L interaction induces in lymphocytes the release of IL-10, which is able to regulate neutrophil trafficking (23). Therefore, a potential effect of the pharmacological blocking of PD-1/PD-1L might be the change of NLR through the regulation of IL-10. The potential value of NLR to follow the evolution of these patients remains to be explored.

The prognostic power of NLR before introduction of immunotherapy has been better studied. Recently, two different studies analyzed the use of NRL as response biomarker in NSCLC patients treated with the PD-1 inhibitor nivolumab: the treatment with this biologic had to be discontinued in patients high NLR before treatment, owing to an accelerated disease progression compared to patients with lower NLR (24,25). High NRL values in these patients could reflect a higher and more extensive tumor activity that could not be controlled by the drug leading to treatment failure.

The studies discussed indicate a clear relationship between inflammation and lung cancer, and establish the prognostic power of NRL in different cancer stages. An interesting question arising from these observations is how NLR compares with other inflammatory markers proposed in the scientific literature. A large study comparing different prognostic markers in a wide range of cancer types was published by Proctor *et al.* (26). In this study, authors focused only in a few blood parameters [C-reactive protein (CRP), albumin, white blood cell (WBC), neutrophil, calcium, lymphocyte and platelet counts] and calculated five different inflammatory scores: prognostic index (PI) (based on CRP and WBC), prognostic nutritional index (PNI) (based on albumin and lymphocyte), platelet/lymphocyte ratio, NLR, and modified Glasgow Prognostic Score (mGPS) (based on CRP and albumin). The study showed that all the scores analyzed, including NLR, were good prognostic markers. These results were interpreted by the authors as evidence that systemic inflammation would be the "common soil" promoting fatal progression in most, if not all, cancers (26).

Altogether, the results discussed indicate that NLR is at least as good prognostic marker as other inflammatory indexes used up to date, but NLR is easy to obtain, non-expensive and his determination is homogeneous among different healthcare resources.

In conclusion, in accordance with Scilla *et al.*, we believe that neutrophil/lymphocyte ratio determined before surgical approach is an excellent prognostic marker in all-stages of NSCLC and in every kind of patients. In our opinion this parameter allows to study more accurately the evolution of NSCLC patients, in order to intensify the targeted treatments or even to plan for a better non-curative medical care. Given the advantages of NLR such as its easy determination, low cost, and ready accessibility in retrospective clinical records, the use of this index as prognosis marker should be considered in common clinical practice in the near future.

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Footnote

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