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Circulating Myeloid-Derived Suppressor Cells and Neutrophil- and Platelet-Lymphocyte Ratio predict clinical efficacy of PD-1/PD-L1 inhibitors in non-small cell lung cancer

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Immune-checkpoint inhibitors (ICIs) are widely used to treat patients with advanced Non-Small Cell Lung Cancer (aNSCLC) who progress after first-line chemotherapy. However, only a subset of patients shows durable response. Despite many efforts, there is still no single validated biomarker for reliable anticipation of ICIs efficacy in both first- and second-line of treatment. There is increasing evidence that Myeloid-Derived Suppressor cells (MDSCs) play important roles in the promotion and progression of lung cancer. Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) are inflammatory biomarkers that have also showed prognostic role in NSCLC. The goal of this study was to evaluate whether pre-treatment circulating MDSCs, NLR and PLR populations could anticipate response to ICIs when used as second-line for NSCLC patients who are refractory to first-line chemotherapy.

We conducted a multi-centric retrospective study including 105 NSCLC patients (stage III-IV) who were treated with second-line ICIs after receiving at least one previous platinum-based combination chemotherapy. The recruited cohort showed the following characteristics: 93% smokers; a median age of 63 years (range 38-80); 60% non-squamous; 81% ECOG PS 0-1 and 50% PD-L1 ? 1%. Median PFS (mPFS) and OS (mOS) was 3.03 months [95% CI, 2.17-6.5] and 11.90 months [95% CI, 8.8-14.43], respectively. Pre-treatment immunophenotyping of cell populations in peripheral blood mononuclear cells (PBMCs) was performed by flow cytometry. Progression-free survival (PFS) and overall survival (OS) was compared by Kaplan-Meier method and Cox Proportional Hazard model. Sperman´s rank or Pearson correlation were assessed between cell populations. Univariate and multivariate Cox proportional hazard models were used to estimate effects of MDSCs and several clinicopathologic factors on OS.

Pre-treatment high level of total MDSCs, defined by the median value as a cut-off (?6.6%), high-NLR, defined by the median value as a cut-off (?4.0), and high-PLR, defined by the median value as a cut-off (?225.0) were significantly correlated with poor OS (MDSCs: p=0.0117, NLR: p=0.0283 and PLR: p=0.0420). Multivariate analysis confirmed that higher NLR and higher total MDSCs levels were also associated with shorter OS (NLR HR 2.35; p=0.01 and total MDSCs HR 2.18; p=0.015).

Our results suggest that elevated levels of MDSCs, NLR and PLR are associated with short-term survival. The predictive power of these markers was increased by categorizing the patients based on whether these 3 cell populations were higher or lower than the median of the cohort, allowing us to draw the conclusion that patients who had these 3 variables below the median showed better PFS and OS. In addition, whereas only 20% of patients with high values had disease progression, more than 80% of all patients with low MDSCs, NLR, and PLR values experienced a full response, a partial response or stable disease. In conclusion, these three cell populations, which are easily determined in blood, could become a valuable biomarker signature for predicting efficacy of second-line ICIs and, therefore, for selecting sensitive patients.