The role of the CXCL12/CXCR4 pathway in the immunotherapy of non-small cell lung cancer

**BACKGROUND**

Peripheral blood mononuclear cells (PBMCs) trafficking is regulated by chemokines, which may interfere with their migration towards tumors and even collaborate in the efficacy of immunotherapy.

In our study, we investigated whether the CXCL12/CXCR4 pathway plays a role in the efficacy of immunotherapy in non-small cell lung cancer (NSCLC) by analyzing the immunophenotypic profile of PBMCs expressing CXCR4 in peripheral blood (PB) and the expression of its ligand CXCL12 in tumor.

**METHODS**

We identified 1, 8, and NK lymphocytes, monocytes, and dendritic cells expressing CXCR4 in PB using flow cytometry in a prospective cohort of NSCLC patients (experimental group) before starting monotherapy with anti-PD-1 immunotherapy.

As a control, we studied patients with advanced cancer before starting any non-immunotherapy treatment.

The relative frequency of immune subpopulations in PB was correlated with treatment outcomes. Patients were classified according to high (above the 55th percentile) or low (below the 45th percentile) expression in PB for each cellular subpopulation.

Un- and multivariate survival analyses were performed using Cox regression and logistic regression.

The expression of CXCL12 in tumor tissue was studied and correlated with the expression of its receptor (CXCR4) in PBMCs.

**RESULTS**

The experimental group included 39 NSCLC patients treated with anti-PD-1 drugs (pembrolizumab/1st line/1st line/2nd line) and the control group included 40 treated with non-immunotherapy drugs. Demographic, clinical, and analytical variables are described in Table 1 and Table 2.

Low expression in PB of CXCR4-expressing CD8+ T lymphocytes was correlated with a higher benefit from immunotherapy. No significant results were obtained in any of the other subpopulations studied.

**CONCLUSIONS**

Patients diagnosed with advanced NSCLC with low expression of cytotoxic T lymphocytes in PB expressing CXCR4 show greater benefit from immunotherapy, probably due to greater tumor infiltration of lymphocytes receiving homing signals from the higher expression of CXCL12 in the tumor.