Examinaton of the immune cells profile of NSCLC patients indicated for inhibitory checkpoint immunotherapy

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Backgroud

Immunotherapy with checkpoint inhibitors is considered a highly potent biologic therapy in selected patients with NSCLC. However, despite the standard biomarker PD-L1, the profile of the ideal candidate for immunotherapy treatment is still not significantly refined. Chronic inflammation may negatively affect the immune response, but the question is how they can modify the course of immunotherapy.
The state of anti-tumor cellular immunity (CD 8+ cytotoxic effector lymphocytes, CD 4+ helper lymphocytes) and the concentration of some immunomodulatory cytokines are gaining an importance and their examination and monitoring are a promising way to find new biomarkers of anti-tumor immunotherapy response and improve its effectiveness.

Goals

The main aim of the study is to determine how to predict more precisely the effectiveness of immunotherapy in patients undergoing immunotherapy with checkpoint inhibitors and to describe possible risk factors for the development of autoimmune reactions in the peripheral blood.

Patients

The research project includes 33 patients who underwent standard oncological treatment for the indication of locally advanced or metastatic NSCLC. The patients were further examined by a clinical immunologist to exclude immunopathology and diseases of the allergic or autoimmune origin.

Methods

Inflammatory parameters (CRP) were measured by Immunoturbidimetry.Antitumor, cellular immunity (CD4 +, CD8 +, B cells) was examined by flow cytometry.

Immune profile

Due to the strong and significant immunomodulatory features of checkpoint inhibitors, a standard, comprehensive immunological examination of a cancer patient is highly desirable. These examinations should provide us with an overview of the condition of the immune system before starting therapy, exclude immunopathological conditions, including severe secondary immunodeficiency, autoimmune or atopic terrain. Before starting immunotherapy, it is advisable to treat immunopathological conditions and restore the immune system to a good condition

Cellular immunity	**Autoimmune panel 2**
Subpopulations of lymhocytes	RF
CD3, CD4, CD8, CD19, NK	RF - IgG, IgA, IgM
	Anti-CCP
Autoimmune panel 1	
CD3, CD4,CD8,CD19,NK,	ANAb IgG
HLA-DR, CD45RA, CD5	ANAb IgA
	ANAb IgM
Immunoglobulins	SMAb
IgG	Myositidy - soubor protilátek
IgA	
IgM	Anti-ENA screen
IgD	V případě pozitivity ENA screen provádíme typizaci protilátek:
IgE	
podtřídy IgG	(SS-A,SS-A/Ro52,SS-B,histon, SM,RNP,SCL-70,JO-1,ribos, PM-SCL100,centroméra B)
	Anti-ds-DNA NIF
	Anti-dsDNA CLIA
Inflammation p.	Anti-nukleosomy
CRP	**Funcional tests, cytokines**
SAA	TNFa, IL-2, IFNy, IL-4
Allergology	IL-10, IL-12
ECP *	IFNy, TNFa, IL-17

Key words
Precision medcine, immunooncology, biomarkers, CD 8 + T lymphocytes

Results

As part of our research project, we divided patients into two groups. These were symmetrical and homogeneous group of patients. The first group consisted of patients with an objective response according to CT examination and some of its patients still continue with immunotherapy. the objective criterion for the inclusion of the patient in the group of responders was, in addition to the objective therapeutic response according to the immunorecist criteria, the completion of at least 15 cycles of immunotherapy. The second group included patients who, according to CT examination, developed rapid disease progression. In our project, we compared the cell populations of immune cells and the basic parameters of systemic inflammation in both groups of patients. Examinations were performed from the peripheral blood of patients and samples were taken before the start of immunotherapy

Figure 1.

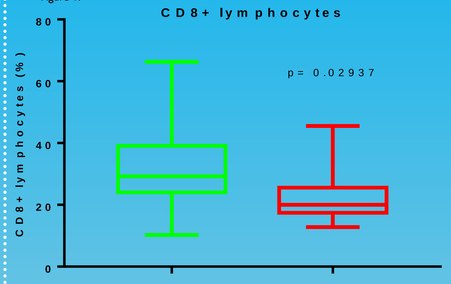


Figure 2.

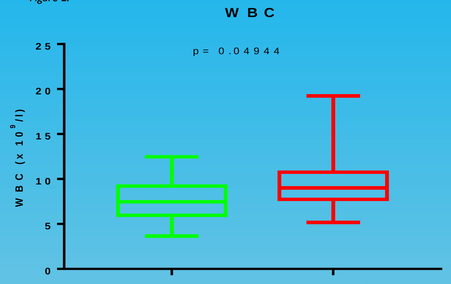


Figure 3.

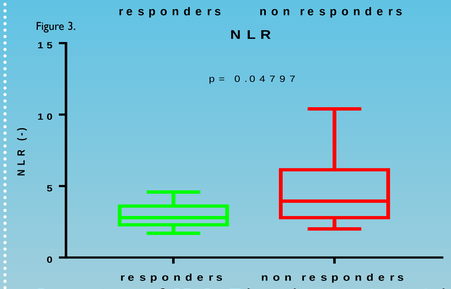
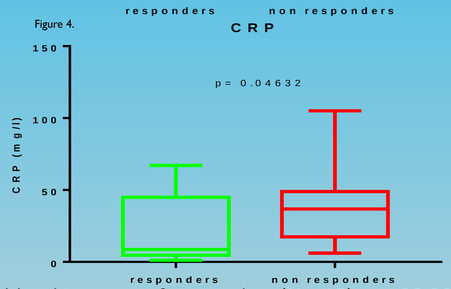


Figure 4.



Percentage of CD 8+ T lymphocytes in peripheral blood in group of responders (N = 15) was 29.20 ±7,10 % and was significantly increased compared to the group of non-responders (N = 18), where we observed median percentage 20.05 ±3.84 % (p = 0.029). There was a significant increase in white blood cells count 9.01 ±1.58 x10^9/l in group of non-responders (N = 18) compared to the group of responders (N = 15), which was 7.4and8 ±1.25 x10^9/l (p = 0.049). Value of NLR ratio in group of non-responders (N = 18) was 3.95 ±1.08 was significantly increased compared to group of responders (N = 15), where we proved median of NRL ratio 2.80 ± 0.54 (p = 0.048). Value of CRP in group of non-responders (N = 18) was 17.4 ±15.07 mg/l and was significantly increased compared to 8.7 ±14.2 mg/l in group of responders (N= 15) (p = 0.046).

Conclusions:

- Our results suggest that if a patient's immune system is in an inflammatory condition prior to initiating immunotherapy, the chances of an objective therapeutic response are reduced.
- High inflammatory parameters and leukocytosis can certainly be caused by other pathological conditions. But higher NLR ratio in the non-responder population suggests, that there may be untreated bacterial inflammation in these patients (such as COPD exacerbations).
- In contrast, patients with normal blood counts and an increased fraction of CD8 + cytotoxic T cells with a physiological or lower NLR ratio appear to be ideal candidates for immunotherapy with checkpoint inhibitors.
- From the results so far, it seems that possible immunomodulation before the start of immunotherapy with proven immunodeficiency or other immunopathology could contribute to the effectiveness of immunotherapy itself.
- Our data could contribute to the tendency to create close collaborations between clinical oncologists and clinical immunologists for the benefit of the oncological patient.