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Early use of steroids affects immune cells and impairs immunotherapy efficacy

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Treatment of patients with non-small cell lung cancer (NSCLC) has been completely redesigned in the last years with the introduction of immune checkpoint blockade (ICB). Antiprogrammed cell death 1 (PD-1) or programmed death-ligand 1 (PD-L1) drugs are currently indicated worldwide for treatment of NSCLC.[1] Known predictive positive biomarkers of response to these agents are PD-L1 expression and tumour mutational burden in tumour samples, but being the overall response rate is only 20%[2] the identification of biomarker of resistance is desperately needed.

The only clinical feature that has represented a common exclusion criteria for all immunotherapy trials is the presence of concomitant diseases that require daily treatment with high-dose corticosteroids.[1] However, patients with NSCLC often receive chronic treatment with a lower dose of corticosteroids, as part of best supportive care, for mitigating symptoms like dyspnoea or fatigue, or encephalic signs in the presence of brain metastasis.

Steroids are known to be immune-suppressive, by impairing T lymphocytes activation, by blocking the expansion of T helper 1 subgroup and favouring the T helper 2 one,[3] by recruitment of T regulatory cells and promotion of M2 macrophage polarisation, and by affecting the microbiome.

Immunotherapy drugs are designed to reawake the cell-mediated side of the immune system to fight cancer; thus, immunotherapy needs an intact and functional immune system to work, and the early changes in antigen presentation and T cells activation correlate with clinical outcome in patients with melanoma treated with immunotherapy.[4] Impairment in this phase of T cell recruitment by early use of steroids, while on ICB, may prevent activation of an effective antitumour immune response. In NSCLC, two evidence derived from real-world clinical scenario is published regarding the relation between the use of steroids and lower progression-free survival (PFS) and overall survival (OS) from anti-PD-1/PD-L1 therapy.[5 6]

In this context, the work by Fuca' *et al*[7] is of great novelty. The authors conducted a retrospective, single-institution cohort study on metastatic NSCLC treated with ICB (96% with single-agent anti-PD-L1), exploring the effect of early use of steroids on clinical outcome and concomitant alterations in peripheral immune blood cells subpopulations. Early use of steroids was defined as 'daily prednisone equivalent dose >10 mg for at least 1 day within 28 days' after the start of ICB. They recruited 151 patients, of whom about half received steroids at any time during the ICB therapy, while 23% met the criteria for early use of steroids. While no difference was found comparing patients receiving steroids at any time during the ICB therapy and never-exposed patients, the early use of steroid was associated with poor disease control rate (34% vs 62%; p=0.006), low PFS (1.98 vs 3.94 months, HR: 1.80; p=0.0003) and OS (4.86 vs 15.14 months, HR: 2.60; p<0.0001).

Within the 'early users' of steroids, the median intake of steroid dose was 280 mg, with a very large range (20–875 mg), and the median time of steroid therapy was 28 days (range 1–28); thus, the effect on clinical outcome is more time-dependent than dose-dependent. The negative effect of early use of steroids on PFS and OS was maintained also in multivariable model analysis, thus reinforcing the casual relation of the data. However, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and tumour PD-L1 level were also independently associated with worse clinical benefit. In this study the early use of steroids was itself associated with ECOG PS >2 and the presence of brain metastasis or metastasis in more than two sites; these clinical features themselves affect the prognosis. Thus, further

prospective studies are needed to quantify the relative contribution of steroids on immunotherapy resistance in these clinically relevant subgroups.

In this regard, Banna *et al*[8] developed a tool to help in choosing between immunotherapy and standard chemotherapy for patients with NSCLC, and among the clinical characteristics they classified ECOG PS ≥1, high neutrophil to lymphocyte ratio (NLR) and concomitant treatment with high-dose steroids as unfavourable for immunotherapy. We foresee in the development of multifactor scores a good instrument to guide patients' selection for immunotherapy.

Furthermore, Fuca' *et al* (in this issue) elegantly showed mechanistically how the early use of steroids impairs the antitumour immune response elicited by immunotherapy. Baseline levels of white cell count, absolute neutrophil count (ANC) and derived NLR (dNLR) were all higher in patients who were under steroid therapy, as expected. In addition, absolute monocyte count, absolute eosinophil count and relative eosinophil count (REC) were also lower in these patients. After 4 weeks neutrophils were even further increased and eosinophil decreased, and after 6 weeks the median absolute lymphocyte count was also significantly lower in the exposed cohort. Among these parameters, NLR ≥5, dNLR ≥3 and REC <1.5 were independently associated with both the early use of steroids and a worse clinical outcome, thus suggesting that the imbalance of immune cells induced by steroids is the intermediate of immunotherapy resistance. High ANC and NLR are the result of the presence of myeloid-derived suppressive cells in tumour site: myeloid cells are actually the topic of many studies and they have a role in immune resistance. The increment of NLR and ANC after steroids has been previously shown only in hormone-resistant prostate cancer,[9] and high NLR itself is a negative prognostic factor also in other cancers, like breast cancer.[10]

Fuca' *et al* show for the first time the positive impact of REC ≥1.5 at 4 and 6 weeks on PFS and OS and its inverse correlation with early use of steroids.

These data are of high clinical value since they encourage the discovery of new biomarkers to identify immune-resistant patients with NSCLC. Nevertheless, with NSCLC being a very complex and heterogeneous scenario, future studies are needed to investigate prospectively the effect of steroids in modulating blood immune cells across different molecular and clinical subgroups of patients and to correlate them to the efficacy of available immunotherapy drugs.

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