Immune-Checkpoint Inhibitors(ICI)

Subjects: Pathology
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Recently, the introduction of immunotherapy radically changed the therapeutic algorithm of non-small-cell lung cancer as upfront or secondary strategy. Unfortunately, the small number of patient who benefits from immune-checkpoint inhibitors (ICI) and the prognostic role of concomitant treatments are a burning open issue. The use of steroids was associated with poor outcomes during ICI. We investigated the impact of intercurrent steroids, according to clinical indication, which is actually unclear. Interestingly, the use of intercurrent steroids given for cancer-unrelated symptoms has no survival impact on our study cohort.

non-small cell lung cancer immunotherapy steroids

1. Introduction

The clinical development of immune-checkpoint inhibitors (ICI) has changed the paradigm of treatment for patients with non-small cell lung cancer (NSCLC)[1]. However, only a limited part of patients benefits from ICI, rising up the need for affordable biomarkers and different therapeutic strategies. Although evaluating the tumor membrane expression of programmed death-ligand 1 (PD-L1) has become mandatory for newly diagnosed advanced NSCLC[2], the ICI as single-agent can achieve satisfying responses regardless of the PD-L1 status in the pretreated population[1].

In addition to tumor biomarkers, other clinical factors have been associated with ICIs outcomes. These factors can potentially influence ICIs efficacy, such as age, Eastern Cooperative Organization performance status (ECOG PS), and concomitant therapies.

Systemic steroids impair the immune system at multiple levels, ranging from the inhibition of acute inflammation to a long-term immunomodulatory effect, and constitute the cross-sectional backbone of the immunosuppressive therapy[3].

In cancer patients, steroids are largely used for treatment of cancer-related symptoms, such as dyspnea, fatigue, anorexia, and symptomatic brain metastasis[4][5][6]. Other conditions, not strictly related to cancer spread, may also require steroids prescription at the beginning or during the anticancer treatments: Exacerbations of chronic

diseases (e.g., chronic obstructive pulmonary disease (COPD), rheumatic diseases, etc.) or toxicities developed under therapies, such as immune-related adverse events (irAEs)[7].

Baseline use of ≥ 10 mg of prednisone equivalents was associated with poor outcomes to ICIs in a large retrospective cohort of pretreated advanced NSCLC, independently from ECOG PS, presence of brain metastasis, or smoking status[8]. In a similar retrospective work, the early introduction of steroids showed a detrimental impact on survival outcomes[9]. Based on these, the use of ≥ 10 mg of prednisone equivalents under ICI has been limited and it is still a classical baseline exclusion criterion from clinical trials.

However, a recent retrospective study revealed that the negative impact of baseline steroids was only observed among patients treated for cancer-related symptoms, more likely related to the palliative condition of this population.[10]. To date, the clinical relevance of the initiation of steroids under ICI according to the reason for prescription remains unknown.

2. Steroids on Clinical Outcomes in Advanced NSCLC Patients under ICI

As far as authors are aware, this is the first study reporting that intercurrent steroids under ICI have no detrimental impact on clinical outcomes when prescribed for non-cancer-related symptoms. In our work, 12% of the patients were treated with intercurrent steroids and experienced poor outcomes (mPFS 1.3 months; mOS 2.2 months). Nevertheless, this negative impact was mainly associated with the prescription for cancer-related symptoms, suggesting that this can be more likely related to the palliative condition of this population, and not with the drug-effect on their immune system. No differences were observed between intercurrent steroids group for cancer-unrelated symptoms (mPFS 2.2 months; mOS 13.4 months) and the no-steroids group (mPFS 2.6 months; mOS 13.8 months).

Daily dose of ≥10 mg of prednisone equivalent has been historically considered an exclusion criterion for clinical trials, mainly based on the increased rate of infections in other chronic diseases, but not on a specific contraindication for cancer patients[11][12][13]. In advanced NSCLC patients, we reported that ≥10 mg use of daily prednisone equivalent at baseline was strongly associated with poor ICI outcomes in a large cohort of 640 patients [8]. However, patients treated with steroids were more commonly associated with poor prognostic factors, such as brain metastasis or ECOG PS ≥ 2, that may also play a role in the negative impact reported.

Based on this hypothesis, Ricciuti et al. studied the clinical impact of baseline-steroids, with the same threshold, according to the reason of prescription in 650 advanced NSCLC patients[10]. In this work, the authors observed that the negative impact of baseline-steroids on outcomes was not confirmed for the subgroup treated for cancer-unrelated indications, questioning the negative predictive role suggested for steroids on ICI treatment[10], which is in line with our data.

Although some previous studies have also investigated the role of intercurrent steroids treatment. Fucà et al.[9] reported worse outcomes in 23% of patients treated with intercurrent steroids (first 28 days) retrospectively studied

on 151 advanced NSCLC patients treated with ICI. Similarly, Drakaki et al.[14] reported that baseline-steroids and intercurrent steroids up to 30 days under ICI (30%) were associated with poor outcomes in a cohort of 862 NSCLC patients. In these two studies, the reason for prescription was not analyzed and the threshold for daily prednisone equivalents differed. Interestingly, Pennell et al. reported at the 2019 World Conference on Lung Cancer (WCLC) the impact of intercurrent steroids on the real-world CancerLinq Discovery Database in 11,143 advanced NSCLC treated with ICI[15]. Among them, 1581 received intercurrent steroids (≥10 mg of prednisone equivalent) within the first 30 days, associated with poor OS. However, when the survival was adjusted by clinical characteristics (age/gender/PS/brain metastasis) no differences were observed in OS, consistently with our findings. The lack of detailed clinical data about the reason for prescription and the appurtenance of a poor prognosis subgroup may confound this statement. In fact, only one experience evidenced this conflict dissecting the clinical indication as palliative or not palliative[10].

Recently, a meta-analysis explored the impact of steroids across 16 studies with melanoma and NSCLC patients [16]. Overall, the patients treated with steroids had a higher risk of both progression and death, but only the intercurrent steroids for palliative purposes were related to the greater risk of death compared to patients receiving steroids for brain metastasis or irAEs. However, the clinical indication was not formally investigated in the majority of the studies enrolled in this meta-analysis. Conversely, the use of steroids for the management of irAEs did not increase the risk of death, as previously described.

The main biological hypothesis of the detrimental impact of steroids under ICI is based on the well-known immunosuppressive effects on both acute and chronic inflammation. The activation of glucocorticoid intracellular receptor (GR) inhibits the innate and adaptive immune response via genomic and non-genomic pathways[2]. Nevertheless, an increasing amount of evidence also shows that steroids can positively induce the innate response stimulating the expression of pattern recognition receptors (PRR), complement components[17], and the production of several cytokines and their receptors such as IL-1, IL-6, TNF, and IFNγ[18]. In light of these data, Cain et al.[17] proposed a biphasic model of immune systems' regulation under the stimulus of steroids that may promote an immune response earlier but shorter with respect to a condition of endogenous steroids deficiency. Whether this model is applicable in cancer patients treated concomitantly with ICI and steroids remains an open issue but evocates possible different biological scenarios, in particular, involving the innate system and myeloid lines.

Consistently, as previously reported, steroids can induce increased absolute neutrophil count (ANC)[19][20][21], and it has been even associated with the polarization of macrophages to M2 macrophages, with pro-tumoral functions [22]. Thus, the global impact of steroids on the immune context of the patients should be further explored.

Although it was not the primary goal of the project, our study showed that the introduction of antibiotic therapy within two months before and one month after the ICI was independently associated with poor outcomes at the multivariate analysis. Interestingly, antibiotics may alter gut microbiota, as suggested by pre-clinical studies conducted on mice models[23]. Moreover, several retrospective analyses[24][25] confirmed the detrimental role of antibiotics in survival outcomes in cohorts of advanced NSCLCs treated with anti-PD-(L)1 inhibitors, albeit the assessment of the underlying mechanisms is still an open issue.

Finally, our findings also confirmed that a deteriorated performance status at baseline (≥2) correlated with poor survival outcomes, as previously described[26]. Notably, Facchinetti et al. evidenced that only a disease burden-induced poor ECOG PS (vs. comorbidities-induced) was independently related with a bad prognosis[27].

Our study has several limitations worthy of discussion. Firstly, the analysis had the intrinsic limitation of a monocentric retrospective experience, with some missing data (e.g., PD-L1 status). In addition, response assessment was not homogenously performed following RECIST v.1.1 criteria with a dedicated radiologist, but the response rate was investigator-assessed, thus resulting less accurate for PFS analysis, the reason why we considered it as secondary endpoint. Finally, the small size of the sample of patients treated for non-cancer-related indications did not allow postulating definitive conclusions.

Despite these limitations, we believe that our work helps to lighten the role of intercurrent steroids in patients treated with ICI. In particular, that the negative impact on clinical outcomes of intercurrent-steroids, as at baseline, is more likely related to the palliative condition of the patients rather than a drug-effect. Thus, steroid prescription should not be avoided under ICI if it is indicated.

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