Editorial

Immune checkpoint inhibitors for non-small cell lung cancer patients on steroid or non-steroidal anti-inflammatory drugs treatment—therapeutic indication or therapeutic efficacy?

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The discovery of immune checkpoint inhibitors (ICIs) has had a major impact on cancer treatment, including lung cancer.

In 1992, Ishida *et al.* identified and named programmed death-1 (PD-1), a molecule and gene whose expression on the surface of T cells is enhanced when T cell death is induced (1). Subsequent studies have shown that PD-1 binds to programmed death-ligand 1 (PD-L1), a molecule on the surface of antigen-presenting cells, and functions to suppress immune responses by T cells (2). Later, it was discovered that many cancer cells express PD-L1 on their surface. These findings revealed that cancer cells bind PD-L1 to PD-1 and suppress the function of T cells, thereby evading the immune system's attempts to eliminate them. Furthermore, Iwai *et al.* showed that blocking PD-L1 could be potential immunotherapy for cancer (3).

In 2015, the therapeutic efficacy of ICI for non-small cell lung cancer (NSCLC) was reported for the first time, as nivolumab significantly prolonged overall survival (OS) compared to docetaxel, the previous standard of care in the second-line treatment of NSCLC (4,5). Subsequently, ICIs were found to be effective in first-line therapy (6), and further development included combination therapy with ICIs and cytotoxic chemotherapy (7-9), as well as combination therapy with two ICIs (10,11). In both treatment modalities, high expression of PD-L1 in cancer tissue tends to be more effective in the treatment of ICI. On the other hand, in the absence of PD-L1 expression in cancer tissue, the therapeutic effect of ICI may not be observed. Therefore, the expression of PD-L1 in lung cancer tissue has a very important role in the choice of therapy.

Svaton *et al.* hypothesized that immune-suppressing drugs, corticosteroids, and non-steroidal anti-inflammatory drugs (NSAIDs), suppress PD-L1 expression in tumor cells (12). The analysis uses a high-reliability database that collects patient data from seven pneumo-oncology departments in the Czech Republic. Patients with stage III–IV NSCLC with known PD-L1 expression from the database were enrolled in this study. 1,148 patients were included in the study, but only 21 patients were excluded. This indicates that a relatively unbiased population was selected. The study investigated whether patients were using corticosteroids or NSAIDs when the biopsy was performed. The patient's corticosteroid comedication counted on the use of more than 10 mg/day of prednisolone. Acetylsalicylic acid was included among the NSAIDs. In this study, the authors did not mention the length of time corticosteroids or NSAIDs were administered. The shorter duration of administration of those drugs is not expected to have a significant impact on the immune status within the tumor. I think it is one of the limitations of this study.

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In this study, 29% of all patients had PD-L1 expression <1%, 41% had PD-L1 expression 1–49%, and 30% had PD-L1 expression >49%. This study had no statistically significant relationship between patient characteristics and PD-L1 expression (12). In general, there are more reports of higher PD-L1 expression with a history of smoking (13-16). I thought this may have happened because the PD-L1 assay in this study was based on a small biopsy specimen, which may have only viewed a part of the tumor and as a result may not have correctly evaluated the expression of PD-L1. In the above regard, I considered that the results of this study need to be carefully interpreted.

In conclusion of this study, neither corticosteroids nor NSAIDs were found to be statistically significantly associated with PD-L1 expression in the current study (12), and the author's hypothesis was rejected. I thought this was good information for patients being treated with corticosteroids or NSAIDs because it meant that their treatment options for advanced NSCLC would not be limited. But this is a separate issue from whether ICIs are effective or not in advanced NSCLC patients treated with corticosteroids or NSAIDs. Patients treated with corticosteroids are often excluded from clinical trials, thus our knowledge on this point is limited. Arbour *et al.* reported on the therapeutic effect of PD-(L)1 inhibitors on patients receiving steroid therapy as a baseline in 2018 (17). In that study, a retrospective review of patients treated with ICIs for advanced NSCLC at Memorial Sloan Kettering Cancer and Gustave Roussy Cancer Center, the group of patients who used more than 10 mg of corticosteroids at baseline had a worse prognosis in both PFS and OS than those who did not. However, most of the reasons for steroid use in that study were mostly for palliation of cancer-related symptoms. Therefore, besides the poor efficacy of ICIs in steroid-using patients, another possible reason for the poor prognosis is that patients with advanced NSCLC who were using steroids may have had more advanced disease than those who were not using steroids. Subsequently, Ricciuti *et al.* conducted a retrospective study of patients treated with ICIs at the Dana-Farber Cancer Institute, comparing cancer-related for palliative indications and cancer-unrelated for nonpalliative indications as reasons for steroid use (18). Patients using steroids for cancer-related palliative indications had a statistically significantly poorer prognosis in OS than patients not using steroids. There was no statistically significant difference in prognosis in OS or PFS in patients using steroids for noncancer-related reasons compared to patients not using steroids. The results suggested that steroid therapy unrelated to cancer symptoms does not affect the therapeutic efficacy of ICIs for non-small cell lung cancer.

In conclusion, Svaton *et al.* showed that high doses of steroids or NSAIDs administered to patients with advanced NSCLC did not affect PD-L1 expression (12). It also showed that treatment with steroids or NSAIDs did not decrease the chance of treatment with ICISs. However, the poor therapeutic efficacy of ICIs has been reported in patients treated with steroids for palliation of cancer symptoms, suggesting that the therapy should be carefully considered in such patients.

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