Non-small cell lung carcinoma: understanding cancer microenvironment to drive immunotherapy and patients’ selection

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Cancer microenvironment, immunotherapy and patients’ selection

Lung cancer is still the first cause of cancer-related death worldwide with non-small cell lung carcinoma (NSCLC) determining approximately 85% of all cases (1). Almost half of lung cancers present with metastases at the diagnosis. Several clinical options have been used, but prognosis remains poor especially in the advanced stages with about 5% of survivors after 5 years (2). Platinum-based chemotherapy remains the standard of care in the first line of treatment, although with a low rate of response ranging between 15-30% (3). In this scenario in the last few years, identification and targeting of programmed cell death-1 (PD-1) and one of its ligands, programmed cell death-ligand 1 (PD-L1), have shown extraordinary results in several cancer types. Consequently, nivolumab and pembrolizumab, two anti-PD-1 agents, has been approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for first- or second-line of therapy in NSCLC.

In a recent issue on Clinical Cancer Research, Mazzaschi et al. (4) report the results of their study, where they evaluated if different tissue immune microenvironments were able to predict survival and response to immune checkpoint inhibitors (ICIs) in NSCLC. The cohort comprised 100 patients undergoing lung resections with curative intent and 26 patients with advanced disease treated with nivolumab in second or third line therapy. Hence, tumor infiltrating lymphocytes (TILs) and PD-1/PD-L1 expression and quantification were assessed. The authors found that NSCLC resected patients with high CD8 lymphocytes lacking PD-1 inhibitor receptor had a longer overall survival and PD-1-to-CD8 ratio was a prognostic factor on both univariate and multivariate analysis. Accordingly, they indicated CD8 lymphocytes lacking PD-1 inhibitor receptor as potential new factor of positive prognosis and survival. The other important findings were that, among patients treated with nivolumab, those with clinical benefit had low PD-1-to-CD8 ratio compared to non-responders and a significant prolonged progression-free survival (median PFS =12.96 vs. 1.84, respectively). Moreover, the incidence and phenotype of TILs differed in squamous cell carcinoma (SCC) versus adenocarcinoma (ADC), in which EGFR and KRAS mutations conditioned a different frequency and tissue localization of lymphocytes. Therefore, some reflections have to be reported, in particular regarding PD-1 as a potential predictive biomarker and selection criterion. In fact, both staining intensity and quantification of positive cells by immunohistochemistry have not still demonstrated consistent results (5). Other issues on PD-1 evaluation include tissue preparation, processing variability, intra-tumor heterogeneity, staining of tumor versus immune cells. Moreover, prior treatments, i.e., radiation or chemotherapy, may also affect PD-1 expression (6). Consequently, it is not surprising that some studies, performed in different types of
cancers, have shown clinical responses also in patients with low or no expression of PD-L1 (7,8).

TILs are a fundamental component of tumor microenvironment and play a significant role in the tumor biology and mediate response to ICI. It is known that a tumor with inflammatory milieu seems better to predict response to ICI. Indeed, such a tumor is characterized by CD8 T-cell infiltration, which leads to the cytotoxic effect typical of T-cell response (9). As a countermeasure tumor cells secrete cytokines, i.e., IL-10, which attract and promote regulatory T-cell (Treg) proliferation and suppress killing CD8 T cell-mediated (10,11). The results of Mazzaschi et al. (4) open an interesting point of view on the inhibition mechanism by ICI. As mentioned above, percentage of patients with good response notwithstanding low PD-L1 expression ranges between 20–25%. This aspect suggests a possible alternative pathway other than PD-1/PD-L1 involved in blocking the inhibition signaling between tumor cells and immune system (12), as appears evident in the Mazzaschi’s cohort where patients with CD8 lymphocytes lacking PD-1 had a better survival compared to others. Additionally, some authors argue that the function of CD8 T-cells having low or intermediate levels of PD-L1 expression is enhanced by selectively PD-1 blockade, whereas CD8 T-cells expressing the highest levels of PD-1 are actually addressed to cell death (13). Therefore, a recent study evaluating the levels of PD-1 on TILs showed no significant correlation between PD-L1 expression in solid tumors and prediction of response to nivolumab (14). As stated by Mazzaschi et al. (4), also the role of other immune cells should be deepened. Myeloid derived suppressor cells (MDSC) are an assortment of non-macrophage cells; the name derived from their myeloid origin and their aptitude to depress T-cell functions. Two types of MDSC have been identified: monocytic MDSC (M-MDSC) and granulocyte polymorphonuclear MDSC (PMN-MDSC). The former in the tumor microenvironment differentiates into immune-suppressive tumor-associated macrophage, the most representative not malignant cells, which favorite tumor progression and inactive innate and adaptive immune response through several mechanisms, as well as PMN-MDSC, a group of cells sharing some characteristics with neutrophils (15). Moreover, in these type of cells it has been demonstrated an over-expression of PD-L1 via hypoxia inducible factor-1α (HIF-1α). Accordingly, combining HIF-1α inhibitors along with PD-L1/PD-1 blockade may be a new tool to enhance immune system in cancer patients (16). However, given the confusing PD-1/PD-L1 results, in our opinion, immunohistochemistry staining may not be considered the best biomarker for therapy with ICI. Other emerging biomarkers that might help predict response to ICI are based on serum or blood-related measurements. In fact, Weber et al. (17) have identified a group of serum proteins, namely acute phase complement and wound healing molecules, expressed in melanoma patients receiving anti-PD-1 antibodies characterized by poor prognosis. Nevertheless, the complexity of interactions between tumor cells, microenvironment and circulating proteins is still far from being completely elucidated and further clinical trials are warranted (Figure 1).

Non-invasive characterization of tumor microenvironment

The abovementioned observations have lead us to search innovative strategies to find out possible new biomarkers of response. In Mazzaschi’s study (4), all patients before lung surgery have performed $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT), an essential imaging modality in diagnosis and staging of lung cancer (27). It might be of particular interest to analyze metabolic PET parameters as possible predictors of survival and response to immunotherapy. FDG uptake, mediated by overexpression of glucose transporter 1 (GLUT1), reflects biological features of tumors, such as proliferation, histologic type, and hypoxia. Additionally, FDG accumulates in tumor-related activated immune cells other than cancer cells (28). Recently, a correlation between metabolic information of FDG and tissue expression of immune markers in patients with NSCLC before surgery was reported (29). In particular, a significant association was found between SUVmax and SUVmean with the expression of CD8-TILs and PD-1-TILs. Moreover, another recent paper by Takada et al. (30) showed a statistically significant association between SUVmax and PD-L1 tumor expression in surgically resected lung cancer, suggesting PD-L1 expression as a malignant feature of the tumor. Indeed, as illustrated by Chang et al. (31) in a mouse model, high glucose consumption by tumors metabolically restricts T-cells, thereby allowing tumor progression. However, standardized methods to define the cut-off values for PET parameters has not yet established and larger sample size studies are needed, as well as tailored response evaluation criteria remain a challenge.

Immune-PET, a molecular imaging based on monoclonal antibodies or antibody fragments labelled with radioactive
elements, represents a novel technique to determine in vivo the expression of cell surface markers of disease. The immune-PET term also includes the use of molecules not implied in targeting checkpoint inhibitors, such as CD3 or CD8 expression on T-cell surface (Figure 1). This innovative non-invasive approach may have a great impact on clinical activity, supporting oncologists in identification, stratification and early evaluation of response to ICI, thus allowing for a better understanding of the mechanisms of response to immunotherapy. On the other hand,
improving the selection of optimal patients could address the economical aspect of immunotherapies, due to the high costs related to the prolonged treatment. However, most of these new immune-PET tracers have been investigated only in pre-clinical settings, so that several questions have to be resolved before application in clinical routine (18-26,32).

In conclusion, in order to better select patients that could benefit from these new drugs, the identification of potential predictive biomarkers represents a continuous challenge in oncology. In our opinion, a combination of cancer biomarkers should be considered. It is possible that different TILs features may have a role in the next future for driving the treatment of NSCLC, but further larger randomized studies are necessary.

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