Clinical significance and implications of immune response in non-small cell lung cancer

Assessment of the host response to cancer provides a unique insight about the host-tumor interaction that is unattainable from radiographic and pathologic information obtained in routine cancer assessment (1). Immune responses within the tumor microenvironment are increasingly implicated as markers of malignant progression and aggression. It has been shown that the host immune response is associated with prognosis in many solid malignancies including melanoma (2), colorectal (3), and ovarian (4), as well as non-small cell lung cancer (NSCLC) (5-9). Interactions between tumor, immune cells, and cytokines can shift the tumor's microenvironment to welcoming or hostile (10). For NSCLC, host immune response has provided prognostic value in stage I patients in whom the value of radiographic and pathologic information starts to reach their limitations. In addition to prognosis, understanding of the tumor-immune microenvironment (TME) is becoming increasingly important with the advent of immunomodulatory therapy.

In this series, we first review the prognostic significance of immune response in early-stage NSCLC patients. With the recommendation of computed tomography (CT) screening for lung cancer, the incidence of early-stage lung cancer is expected to increase (11). For patients with stage I NSCLC, surgical resection to remove the lung containing the tumor and the regional lymph nodes is considered the standard of care (12). Despite being considered stage I, 1 in 4 patients experiences recurrence within 5 years (13). One of the limitations of the current TNM (tumor, node, metastasis) staging system is the lack of ability to stratify clinical outcome in T1N0M0 patients. Akpoviroro *et al*. first review the published knowledge about the prognostic significance of the TME that is made of tumor-infiltrating immune cells and cytokines. We learn that not all immune responses are necessarily anti-tumor and that for tumor-infiltrating immune cells, these should be assessed with regards to their type (pro- or anti-tumor), location (intra-tumoral or stromal), and density (3). We then review how the TME can be assessed pathologically. Zheng *et al*. review the immunohistochemical markers for each cell type and how they are assessed pathologically. While digital assessment of tumor-infiltrating immune cells has been performed in colon cancer (14), majority of work in NSCLC remain by subjective analysis and thus represents a potential area of future work. In addition to the tumor-infiltrating immune cells, the tumor-draining lymph nodes (TDLN) warrant investigation. TDLN is the site in which antitumor immune responses are initiated (15) and is the preferential site of initial tumor metastases (16). Lin first reviews the published work on both clinical and animal studies investigating the unique lymphatic drainage pattern of lung cancer that does not always follow a well-established drainage pattern seen in breast cancer and melanoma. Sridhar *et al*. then review the literature on immune cell make-up in TDLN and its prognostic significance in NSCLC. The review shows that while regulatory T-cells in the TDLN seems to portend poor prognosis (15), more work needs to be done in assessing this area specifically in stage I NSCLC population. Beyond TME and TDLN, the host-tumor interaction may also be reflected in the peripheral blood (17), and the prognostic significance of immune make-up in the peripheral blood has been widely investigated in many cancers. Asokan *et al*. review what is known in NSCLC. By reviewing TME, TDLN, and peripheral blood, one starts to fully understand the host immune response as a whole.

It is just as important to understand the host immune response as it is to understand the tumor side of the host-tumor interaction. Takahashi *et al.* provide insight into neo-antigens and the immune response elicited by them as they pertain to NSCLC. Better understanding of neo-antigens may allow us to leverage these findings into potential treatment strategies, an issue that is more so important with the advent of immunotherapy. While there is now ample evidence on efficacy of immunotherapy in advanced stage NSCLC patients, Chan *et al.* review the published experience on immunotherapy given as neoadjuvant therapy in stage I NSCLC patients.

Better understanding of the immune response in NSCLC has both prognostic as well as potential therapeutic implications. In this series, we comprehensively review what is known on the host immune response from TME, TDLN, and peripheral blood aspects and also review what is known on the tumor side. With CT screening for lung cancer, incidence of stage I NSCLC and smaller tumors are expected to increase, and inevitably, the TNM staging system will be limited in assessing these small, node-negative tumors. From prognostication standpoint, immune response offers an intriguing option as a potential additional prognostic marker. In colorectal cancer, the prognostic value of immune response has led some groups to introduce

the idea of an "Immunoscore" and a TNM-I staging system to integrate the host immune/inflammatory response (18). From therapeutic standpoint, a better understanding of the tumor-immune interaction will allow us to better strategize further advancement in immunotherapy. Understanding the immune response in NSCLC has important implication from both prognostic as well as therapeutic standpoints.

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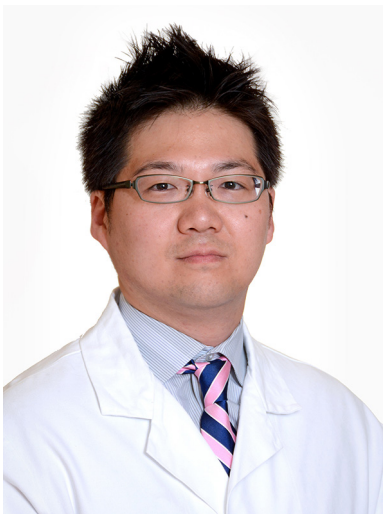

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