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Possibility of Using the Interferon Gamma Release Level As a Dynamic Biomarker

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Commentary

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ABSTRACT

The potential of using interferon-γ (IFN-γ) release as a biomarker was examined in the previous study. Twenty-nine patients treated with immune checkpoint inhibitors were divided into three groups according to their IFN-γ release level in the positive control after enzyme-linked immunosorbent assay. The three groups showed clear differences in clinical outcomes. IGR can be a new dynamic biomarker to determine the immunological status of a patient at the pretreatment stage or any change in the state of their immunity during the treatment of various diseases.

COMMENTARY

Several studies [1-3] have reported that the programmed cell death 1 (PD-1)/PD-1 ligand 1 (PD-L1) axis and interferon-gamma (IFN-γ) are important for acquiring cellular immunity to Mcobacterium Tuberculosis (TB pathogen). In the previous study [4], we attempted to verify the hypothesis that there are changes in the IFN-γ release (IGR) after immune checkpoint inhibitor treatment (ICI-tx) and also examined the usefulness of IGR as a biomarker. IGR was measured using enzyme-linked immunosorbent assay [QuantiFERON®-TB Gold Plus (QFT-TB)]. Based on the IFN-γ levels in the positive control, identified by a response to phytohemagglutinin (PHA), 29 patients with non-small-cell lung cancer (NSCLC) enrolled in the our study were divided into three groups: Group-1 (n=8), consisting of patients with <10 IU/ml at pretreatment, Group-2 (n=12) which included patients who displayed a decrease in the IFN-γ level to <10 IU/ml during ICI-tx, and Group-3 (n=9) where the IFN-γ levels in patients did not decrease below 10 IU/ml even after treatment. Group-1 tended to have higher levels of both neutrophil-to-lymphocyte ratio and C-reactive protein, and lower levels of both body mass index and serum albumin, than the other groups. Group-1 may have a poor immunological status, including cancer-associated inflammation and malnutrition, as described in our previous study [5]. Early progression and ICI-induced interstitial pneumonitis were frequently observed in Group-1 and Group-2, respectively. Group-3 exhibited more treatment cycles than the other groups. Subsequently, we concluded that IFN-γ levels could be a biomarker for ICI-Tx.

Huang et al. [6] reported that a higher pre-treatment PHA-stimulated IFN-γ response (High-PHA) was associated with better survival among advanced NSCLC patients treated with chemotherapy. This result was similar to that of our recent study [7], which

indicated High-PHA, which may reflect a better immunological status, was associated with better progression free survival. Yong et al. [8] reported that low IFN-γ response to PHA in the Quantiferon®-Cytomegalovirus at the 3-month time-point following allogeneic hematopoietic stem cell transplantation was predictive of reduced 12-month overall survival, increased non-relapse mortality, and reduced survival in recipients with acute graft versus host disease (GVHD). This result was similar to our previous study [4] that the reduction of response to PHA after ICI-tx was correlated with both poor treatment outcomes and ICI-induced interstitial pneumonitis. In our recent study [7], we explained that common post-treatment reduction is observed in the following scenarios: 1) As a cytotoxic T-Cell (CTL) in GVHD recognizes a specific antigen in the recipients, it will display a low response to any non-specific stimulation from PHA; 2) ICI-tx would promote T-Cell to differentiate into a CTL that respond to specific antigen and, subsequently, may remove non-specific response for PHA. Therefore, we speculated that a decrease in the IFN-γ levels in patients with immune-related adverse events may resemble the loss of response for PHA in severe GVHD. Thomason et al. [9] suggested that elevated IGR in the negative control of the QFT-TB assay may offer a readily available tool in the form of a biomarker for assessing the disease activity in patients with systemic lupus erythematosus. Furthermore, in future, if cancer-antigen [10] in substitution for TB antigen could be used on QFT-TB, prediction of ICI-tx efficacy may become possible by improved QFT-TB.

Thus, IGR can be a dynamic biomarker to detect the immunological status at pretreatment or the change in the state of immunity during various diseases.

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