Thoracic Cancer
Open Access
Thoracic Cancer ISSN 1759-7706

EDITORIAL

Equibalancing immune-related adverse events and anticancer activity of immune checkpoint inhibitors

Immune checkpoints represent a fundamental self-regulating function of the immune system overseeing and preventing excessive activation or deleterious immune responses, thereby ensuring that our own immune system does not harm ourselves, as a host. Of the most investigated mechanistic pathways through which the immune system self-regulate is the cytotoxic T-lymphocyte antigen 4 (CTLA4) and the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway.[1] CTLA4 usually resides intracellularly and after activation by T cells, they are translocated on the cell surface membrane. PD-1 is a protein that is upregulated on the cell surface of T cells, while PD-L1 is often expressed in the tumor microenvironment on cancer cells, T cells, B cells, antigen presenting cells (APCs) and more. Briefly, if the PD-1 on T cells cannot identify and bind to a PD-L1 on other cells, this will trigger an immune response to kill that cell and tumors are able to escape the immune system by expressing PD-L1. However, immune checkpoint inhibitors are able to suppress this PD-1/PD-L1 or CTLA4/B7 interaction between the immune cells and cancer cells, thereby triggering an immune response to kill the unrecognized cancerous cells.[2]

Until recently, several immune checkpoint inhibitors have been approved by the Food and Drug Administration, namely nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab and ipilimumab. They have shown efficacies in several cancers, including melanoma (ipilimumab, nivolumab, pembrolizumab), non-small cell lung cancer (nivolumab, pembrolizumab, atezolizumab), urothelial cancer (nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab), classic Hodgkin's lymphoma (nivolumab, pembrolizumab) and more. Suppression of the CTLA4 and PD1 pathways allows tumor-specific T cells to expand and promotes antitumor activity.

The main dilemma is that these immune proteins also exist in noncancerous tissues such as endothelium, intestines and heart with many as yet undiscovered.[3] Although we can stimulate the expansion of T cells, we are still not able to fully control the extent of this expansion, thereby leading to undesirable adverse events which can affect any bodily organ. These adverse events can range from mild to fatal, mostly depending on the organ(s) involved and the severity of the reactions. They can occur at any time after treatment initiation but usually appear in the first few weeks to months after treatment, or treatment discontinuation. To complicate things, the adverse events of those treated with anti-CTLA4 therapy differs from those treated with anti-PD-1.[4] In contrast, those of anti-CTLA4 tend to be more severe. The underlying precise pathophysiology of these immune-related events and differences are yet to be elucidated, but it is believed that the host genetics and microbiota play important roles.[5–7]

In a recent article by Yang *et al.*[8] entitled "Management of Adverse Events in Cancer Patients Treated With PD-1/PD-L1 Blockade: Focus on Asian Populations," the authors elaborately reviewed the different types of immune-related adverse events and their potential corresponding treatments by mainly focusing on Asian patients. They reported that the range of immune-related adverse events (irAEs) in Asian populations can range from 12% to 90% and that the type of irAEs experienced differs among different malignancies; possibly related to the sites of action or organs where T-cell aggregation have been occurred. The mainstay of irAEs treatments are the use of immunosuppressive agents. Glucocorticoids are usually used as the first-line for immunosuppressive agent and if not initially effective, additional agents can be used. Based on the AEs gradings of the Common Terminology Criteria for Adverse Events (CTCAE) and the recommendations of the American Society of Clinical Oncology, patients found to have grade 1 irAEs can continue therapy, but under close monitoring. For grade 2 irAEs, therapy should be suspended, but can be continued if the symptoms or laboratory results regress to grade ≤ 1. For grade 3 irAEs, therapy should be suspended, high-dose corticosteroids should be initiated and if patients' conditions do not ameliorate within 2–3 days, treatment with infliximab should be considered. For those with grade 4 irAEs, permanent discontinuation of the immune therapy is advised, except for endocrine abnormalities that have shown amelioration with hormone replacement therapy.

Finding the optimal management of irAEs is difficult as they may affect a wide spectrum of body organs and tissues despite numerous efforts in immuno-oncology research to fight cancer. Management efforts still rely on the clinical experience of the treating physicians, although collaboration via multidisciplinary team would be more

effective, especially when dealing with rare but potentially life-threatening irAEs, such as myocarditis and pneumonitis, as until recently there have been no prospective clinical trials defining the best irAEs treatment approaches.[9] One possible alternative would be simulating these conditions using animal models capable of mimicking the human immune microenvironment, but this has been very challenging to date and is still at the investigation stage[10]

Unlike in other forms of therapies in which disease progression can result when treatment is stopped due to, or for treating the related AEs, the use of immunosuppressive agents in treating irAEs did not show any differences in antitumor efficacy between those requiring and not requiring them, although precautions for opportunistic infections should be carefully assessed. The safety implications to restart immunotherapy after regression of the irAEs and the optimal time to restart them, or whether a "watch and wait" strategy would be applicable have not been prospectively investigated but retrospective analyses have suggested that irAEs associated with one class of agent may not recur during subsequent treatment with another agent.[6,11]

In summary, immunotherapy can be viewed as a double-edged sword. With regard to tumor heterogeneity, the reinforcement of a patient's own immune system to combat his/her own cancer is a major milestone for individualized cancer treatment, but the main focus should still be on maintaining the equilibrium between the control of irAEs and maintenance of antitumor efficacy. Close surveillance of patients must be emphasized for early identification of the irAEs and timely intervention as usually these irAEs are not life-threatening and tend to be manageable.

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