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Immune Check Point Inhibitors in Cancer Therapy: Beware of "Friendly Fire" Effect

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Editorial

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Immune check point inhibitors (ICPI) have revolutionized cancer therapy by their impressive survival benefit and tolerable safety profile. To date, FDA-approved immune check point inhibitors include: cytotoxic T-lymphocyte associated protein (CTLA-4) inhibitors (iplimumab) and programmed cell death/ligand (PD-1/PD-L1) inhibitors (tremelimumab, pembrolizumab, nivolumab and atezolimumab). Several other agents are currently being evaluated in tertiary care centers via clinical trials [1]. Based on the randomized trials and clinical experience, the toxicity profiles of ICPIs are different from that of traditional cytotoxic chemotherapies or molecular targeted agents. Generally, PD-1/PD-L1 inhibitors are considered much safer compared to that of CTLA-4 inhibitors, which can be partly explained by their different mechanism of action. The PD-1/PD-L1 pathway is commonly activated by cancer cells in the tumor microenvironment and blocking the PD-L1 pathway by PD-1/PD-L1 inhibitors is more specific and tumor selective; thus making the side effects less frequent and less severe [2]. On the contrary, the CTLA-4 pathway involves regulating T-cell priming in secondary lymphoid organs and its blocking leads to more systemic side effects [3].

Immunologic checkpoints are an essential component of the immune system, and interfering with these natural checkpoints can result in aberrant immune activation, leading to undesirable off-target inflammation and autoimmunity damaging the innocent host cells, termed the "friendly fire" effect. "Friendly fire" is a military term that typically describes the risks to troops from their own weaponry during combat operations. Like "friendly fire" effect in military, immune-related adverse events (irAEs) can affect various organs in host ranging from mild to life-threatening consequences. Because of this, some patients require permanent discontinuation of treatment. Moreover, moderate to severe side effects potentially need long courses of steroids or infliximab (tumor necrosis alpha blocker) therapy.

Immune checkpoint blockade can lead to the breakdown of immune self-tolerance, thereby inducing a novel syndrome of autoimmune/auto-inflammatory side effects, designated as "immune-related adverse events," mainly including rash, pneumonitis, colitis, hepatitis, cardiotoxicity and endocrinopathies [4-10]. The spectrum of endocrine related adverse events includes acute immune mediated hypophysitis (IH) and hypopituitarism, thyroid disease or abnormalities in thyroid function tests (TFTs). Other endocrinopathies, such as primary adrenal insufficiency, hypogonadism, hypercalcemia, primary hypoparathyroidism, and type 1 diabetes mellitus, have been reported as well, but are rare. The prevalence of endocrine related adverse events varies with the type of immunotherapy used. Based on our clinical experience at the NIH and a meta-analysis, hypophysitis is the most commonly observed side effect with anti–CTLA-4 agents and anti–PD-1 antibodies are generally associated with altered thyroid function tests. Adrenal insufficiency secondary to hypophysitis, if not promptly recognized, may be life-threatening. Hypopituitarism caused by these agents is rarely reversible, and requires long-term substitutive hormonal treatment.

Several case reports have described a wide spectrum of side effects of ICPIs involving the neurological, gastrointestinal, renal and cardiovascular systems. Observation of autoimmune/auto-inflammatory and organ system side effects, while traditionally undesired, indicates that the host system and cancer are responding to the immunotherapy. However, currently

there are no good predictors for toxicity due to these check point inhibitors. Additionally, there are no guidelines on the treatment and monitoring of patients with immune-related adverse events. Therefore, identification of patients at risk, frequent monitoring, two-way communication between patients and comprehensive care team, early recognition and treatment of irAEs are critical in optimizing treatment outcomes. The prescribing medical oncologist should be aware of the irAE profile of each drug, and early consultation with other specialties is critical to maximize successful management of these side effects. In general, mild toxicity does not warrant medication discontinuation, but treatment of moderate or severe irAEs requires interruption of the checkpoint inhibitor and/or use of immunosuppressive agents (corticosteroids and infliximab). For grade 2 toxicities, the ICPIs are to be withheld and should only be resumed after toxicities are resolved or at least decreased to grade 1. If grade 2 side effects persist more than a week, prednisone 0.5 mg/kg/day should be initiated. If side effects persist on corticosteroid therapy (3 or more days), it is advisable to switch to infliximab (tumor necrosis alpha blocker). For severe or life threatening toxicities, the ICPIs are to be permanently discontinued. High doses of prednisone (1 mg/kg/day) or equivalent should be used to treat the severe side effects. Infliximab is reserved for severe and refractory cases [11,12].

In our view, before initiating a patient on ICPI therapy, a comprehensive care team should carefully weigh the risks and benefits of therapy. For a patient fighting cancer, the possibility of having to discontinue ICPI due to side effects may contribute to a feeling of defeat in the face of a chronic debilitating condition; As these agents are known for their peculiar form of toxicities, the comprehensive care team should include highly competent oncologists, internists and other sub-specialists who are aware of the “friendly fire effect” of these agents. As described above, ICPIs have the potential to involve any organ system in the body and collaboration among different medical subspecialties like endocrinology is highly warranted to deliver optimal care to patients treated with ICPIs.

Health care professionals need to be educated on the potential side effects of ICPIs such that early recognition and treatment can be initiated, thereby improving the quality of life and survival of cancer patients on ICPI therapy. Formulation of guidelines for early detection and the optimal management of side effects induced by these immune checkpoint inhibitors should be areas of further work in forthcoming years. Most importantly, we need better insight on the effects of ICPIs on normal tissues, so that potential adverse side effects can be predicted based on their selectivity profile. As these novel chemotherapy agents arise, we must devote time, training, and further investigations to ensure we are providing the best care for our patients.

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