BMH MEDICAL JOURNAL

BMH Med. J. 2019;6(3):78-80. **Editorial**

Immune Checkpoint Inhibitors and Myocarditis

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Abstract

Immune checkpoint inhibitors (ICI) are a promising group of novel anti cancer drugs. They are monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1) and its ligand (PD-L1). This group of drugs have been useful in a wide variety of malignancies with an otherwise poor prognosis. Important drugs in this class are ipilimumab, nivolumab, pembrolizumab and atezolizumab. Though they are excellent therapeutic options in several malignancies, some immune-related adverse effects have been noted, of which autoimmune myocarditis is potentially life threatening. Pathology of ICI-associated myocarditis is characterized by intense infiltration by T lymphocytes and macrophages. Severe myocarditis will mandate suspension of ICI treatment and initiation of high dose corticosteroids (prednisolone or methylprednisolone).

Keywords: Immune Checkpoint Inhibitors, Myocarditis

Myocardial dysfunction leading to heart failure is one of the well known adverse effects of cancer chemotherapy, especially with anthracycline group of drugs [1]. Immune checkpoint inhibitors (ICI) are a promising group of novel anti cancer drugs. They are monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1) and its ligand (PD-L1). This group of drugs have been useful in a wide variety of malignancies with an otherwise poor prognosis. Important drugs in this class are ipilimumab, nivolumab, pembrolizumab and atezolizumab [2]. Though they are excellent therapeutic options in several malignancies, some immune-related adverse effects have been noted, of which autoimmune myocarditis is potentially life threatening [3].

Anti-CTLA-4 monoclonal antibodies were the first generation ICIs. Ipilimumab was the prototype of this class of monoclonal antibodies. Anti-PD-1 monoclonal antibodies were the second generation. Nivolumab and pembrolizumab target PD-1 while atezolizumab, avelumab and durvalumab target PD-L1 [2]. Therapeutic blockade of immune checkpoints by these drugs can alter immunological

tolerance and give rise to autoimmune or inflammatory side effects known collectively as 'immune-related adverse events'. Of these, endocrinopathies involving the thyroid and pituitary have high risk of irreversible toxicity. Cardiac immune-related adverse events are less common than those which affect other organ systems.

PD-1 is expressed in human hearts as well as in the hearts of mice. PD-1 deficiency has been shown to produce fatal myocarditis in certain types of mice [4]. Though myocarditis is a rare adverse effect of ICIs, due to the increasing number of cancers being treated with these drugs, the chance of occurrence of myocarditis is also increasing. But due to the low prevalence, it has been difficult to assess ICI-associated myocarditis in any single clinical trial. Hence Checkpoint Inhibitor Safety Working Group has recently conducted a workshop and summarized their findings and proposed steps [5].

Pathology of ICI-associated myocarditis is characterized by intense infiltration by T lymphocytes and macrophages [6]. The rather rapid onset of myocarditis after initiation of ICIs would also suggest the presence of a pre-existing factor that was held in check by the pathway targeted by the treatment [5]. ICI-associated myocarditis occurs early during treatment and is more common with combination ICI, though two thirds of cases occurred following monotherapy [7].

American Society of Clinical Oncology Clinical Practice Guideline has addressed the management of immune-related adverse events in patients treated with ICIs including myocarditis [8]. The symptoms to look for include chest pain, palpitations, peripheral edema, fatigue and breathlessness. Baseline evaluation would include and ECG and cardiac troponin estimation. Additional testing based on symptoms may be echocardiogram, chest X-ray and B-type natriuretic peptide estimation. Cardiac magnetic resonance imaging (CMR) with late gadolinium enhancement may be considered in selected cases. Cardiac catheterization is useful in assessing the hemodynamic status and histological documentation of myocarditis with endomyocardial biopsy.

Severe myocarditis will mandate suspension of ICI treatment and initiation of high dose corticosteroids (prednisolone or methylprednisolone). Tapering of corticosteroids is done over a course of 4 to 6 weeks. In refractory cases addition of mycophenolate, infliximab or antithymocyte globulin may be considered [9].

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