Florida CHAPTER

Immune Check Point Inhibitors

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CANCER BACKGROUND

Immune check point inhibitors (ICIs) have revolutionized the treatment of cancer. ICIs are antibodies that block negative regulators of the T cell immune response by turning off T cell inhibitor receptors including CTLA4, PD1 and PDL1 receptors and "unleashing" the immune system. They have a significant mortality benefit in numerous cancers, but the augmented immune response leads to a range of autoimmune disorders including cardiovascular toxicity. Currently approved for melanoma, Merkel Cell carcinoma, lung, liver, head and neck, renal cell and triple negative breast cancers among others. There are 7 FDA approved ICIs: ipilimumab (Hervey), pembrolizumab (Keytruda), nivolumab (Opdivo), atezolizumab (Tecentriq), avelumab (Bavencio), durvalumab (Imfinzi), cemiplimab (Libtayo).

ADVERSE EFFECTS

While the incidence of ICI myocarditis is low (1-2%), there are currently more than 600,000 patients/year treated with ICIs and more than 1 million/year predicted in the near future, so there is a potential for > 10,000 cases per year of ICIs myocarditis. The most common ICIs cardiac side effects are myocarditis (50 % mortality), pericarditis (21 % mortality) and vasculitis (6% mortality).

RECOMMENDATIONS

Diagnosis and treatment: Myocarditis can present with chest pain, dyspnea, tachy or brady arrhythmias and commonly occurs early after receiving ICI (median 34 days). Most patients have abnormal ECG (89%), and/or positive troponin (94 %). Echocardiogram can be normal in 50 % of affected patients. Cardiac MRI shows late gadolinium enhancement, patchy myocarditis and definitive diagnosis is obtained by endo-myocardial biopsy lymphocytic infiltrates. Diagnosis of possible, probable or definitive ICI myocarditis is based on the number of clinical, ECG, biomarkers, MRI and biopsy elements. Treatment includes high doses of methylprednisolone (1 gr/day) and in refractory cases additional drugs like infliximab, IV immunoglobulin. Surveillance in high risk patients can be considered with baseline ECG and troponin and weekly troponin for first six weeks.

DATA TO SUPPORT

Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol. 2018;71(16):1755–1764. doi:10.1016/j.jacc.2018.02.037

Ganatra S., Neilan T.G. Immune checkpoint inhibitor-associated myocarditis. Oncologist. 2018; 23:879–886

INDICATIONS

ICIs have been very effective for treatment of advanced metastatic cancers including melanoma, non-small cell lung cancer, renal cell carcinoma, head and neck squamous cell carcinoma, urothelial cancer, refractory Hodgkin's lymphoma, refractory triple negative breast cancer amongst others. These indications continue to expand and the incidence of cardiotoxicity is expected to grow.

ONCOLOGY COMMENTS

Non cardiac toxicities are quite common: fatigue in 16-40 % of patients, along with dermatitis like eczema, multiple rashes and Stevens-Johnson syndrome can occur. Severe diarrhea and colitis that may require hospitalization and IV hydration. Hypothyroidism, hypophysis insufficiency and adrenal insufficiency can be lifelong (as opposed to other immune related adverse effects). Pneumonitis can be life threatening. Neuropathies, Guillain Barre-like syndrome and severe ocular toxicities can occur. Most of the severe forms of ICIs toxicities are treated with high dose steroids and discontinuation of ICIs.