Title

Cardiac Toxicity Associated with Checkpoint Inhibitor Immunotherapy

Journal

Proceedings of UCLA Health, 24(1)

Authors

Kim, David D.
Shin, David

Publication Date

2020-11-09

CLINICAL VIGNETTE

Cardiac Toxicity Associated with Checkpoint Inhibitor Immunotherapy

David D. Kim, MD and David Shin, MD

Case Report

A 57-year-old woman who never smoked was diagnosed with metastatic lung adenocarcinoma with an epidermal growth factor receptor (EGFR) mutation (exon 19 deletion) in 2013 after presenting with a right upper lung mass and bone metastases. She was treated with an oral tyrosine kinase inhibitor (TKI), erlotinib, and had a partial response to therapy. After almost 2 years of erlotinib, she had cancer progression with the emergence of the EGFR T790M mutation. She was enrolled in a clinical trial of a novel TKI known to have activity in T790M-mutated lung cancer. After a partial response and almost 1 year on the clinical trial, she developed an asymptomatic solitary brain metastasis and stopped trial therapy. She started osimertinib, another TKI active against the T790M mutation, with complete response of her brain metastasis. She was treated with osimertinib for approximately 2 years. During this time, her primary right lung tumor was treated with stereotactic body radiation therapy for growth without progression in other sites of cancer. In 2018, she was started on carboplatin, paclitaxel, bevacizumab, and atezolizumab for further progression of her right lung tumor. Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF) and inhibits tumor angiogenesis. Atezolizumab is a monoclonal antibody against programmed death-ligand 1 (PD-L1) and functions as an immune checkpoint inhibitor. Her sites of cancer remained stable on this regimen and she was transitioned to maintenance therapy with bevacizumab and atezolizumab without cytotoxic chemotherapy. After 9 months from initiation of bevacizumab and atezolizumab, she was admitted to an outside hospital for acute shortness of breath and found to have hypotension and pulmonary edema on chest X-ray. She required intubation, mechanical ventilation, and dopamine drip for respiratory failure and cardiogenic shock. Echocardiogram revealed severe global hypokinesis with a left ventricular ejection fraction (LVEF) of 10-15%, compared to a normal baseline echocardiogram. Troponin T was 0.05 ng/mL. Infectious work-up, including blood cultures, was negative for sepsis. Cardiac toxicity from immunotherapy was suspected by Cardiology. She was treated with methylprednisolone 1000 mg IV and was extubated the day after intubation. After several days of high-dose steroids, she remained weak and dependent on supplemental oxygen with a repeat LVEF on echo of 10-20%. She was treated with 1 dose of infliximab 5 mg/kg IV and clinically improved. She was eventually discharged on a slow prednisone taper as well as lisinopril, carvedilol and spironolactone. She was referred to Cardio-oncology as an outpatient. Cardiac MRI revealed no abnormal delayed enhancement to suggest myocarditis. The appearance was suggestive of nonspecific cardiomyopathy. CT coronary angiogram revealed no significant coronary artery stenosis. Over the next month, her LVEF improved to over 45% and her activity tolerance returned close to her baseline. Bevacizumab and atezolizumab were discontinued.

Discussion

In 2020, an estimated 228,820 people will be diagnosed with lung cancer and an estimated 135,720 people will die from lung cancer in the United States. Lung cancer is the leading cause of cancer deaths in both men and women in the US.[1] The treatment of advanced lung cancer has come a long way over the last two decades, before which only cytotoxic chemotherapy was available. During this time, targeted therapies such as EGFR and ALK tyrosine kinase inhibitors and angiogenesis inhibitors of the VEGF pathway were added to the armamentarium. The most recent breakthrough in lung cancer therapy has been immune checkpoint inhibitors. Nivolumab was the first immunotherapy to be approved for the treatment of advanced lung cancer by the FDA in 2015 after it was shown to improve survival over chemotherapy in the second-line setting. Since then, immune checkpoint inhibitors, originally FDA-approved for advanced melanoma, have been found to be active against many other cancer types, including renal cell cancer, lymphoma, head and neck squamous cell cancer, liver cancer, bladder cancer, gastroesophageal cancer, and micro-satellite instability-high cancers in the first or second-line settings.[2] In general, the benefits of immunotherapy have been excellent tolerability compared to chemotherapy and durable responses in many tumor types.

Immune checkpoint inhibitors activate the patient's own T-cell immune response against tumor cells which previously evaded immune surveillance by suppressing an immune response against them. This immune activation is achieved by inhibiting immune checkpoint proteins involved in restraining the immune response. Immune checkpoint proteins cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are inhibitory receptors present on cytotoxic T cells and programmed death-ligand 1 (PD-L1) is present on tumor cells. These proteins are targeted using monoclonal antibodies. Examples of immune checkpoint inhibitors include anti-CTLA-4 antibodies (ipilimumab), anti-PD-1

antibodies (nivolumab, pembrolizumab), and anti-PD-L1 antibodies (atezolizumab, avelumab, and durvalumab). Activation of the immune response against tumor cells can lead to unwanted side effects from immune attack of normal tissue. Since the first trials of immune checkpoint inhibitors on humans, a variety of immune-related adverse effects involving almost every organ have been documented, including inflammatory dermatitis, colitis, hepatitis, pneumonitis, hypothyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, inflammatory arthritis, nephritis, myasthenia gravis, neuropathy, encephalitis, autoimmune hemolytic anemia, and immune thrombocytopenia.[3]

Among the first reports of immune-related cardiac toxicity from immune checkpoint inhibitors included two cases reported by Johnson et al.[4] They were both patients with metastatic melanoma treated with the combination of nivolumab and ipilimumab, who presented with fatigue and shortness of breath. Evaluation revealed abnormal EKG changes and elevated creatine kinase-myocardial band (CK-MB) and troponin I levels. They were diagnosed with myocarditis and eventually died despite immunosuppressive therapy. Post mortem pathology revealed T-cell lymphocytic infiltration within the myocardium and within melanoma metastases in both patients. The mechanism of immune myocarditis was speculated to be shared or similar antigen between the myocardial and tumor cells recognized by clonal T-cells. Of note, there was increased expression of PD-L1 in injured myocardial cells. Johnson et al also analyzed myocarditis in a population of 20,594 study patients treated with nivolumab, ipilimumab, or both, and found myocarditis in 0.09%. The combination of nivolumab and ipilimumab was associated with more frequent (0.27%) and more severe myocarditis than nivolumab alone (0.06%). A multi-center registry study of patients treated with immune checkpoint inhibitors reported the prevalence of myocarditis was 1.14% with a median onset of 34 days from initiating immune checkpoint inhibitors. Tropinin was elevated in 94% and LVEF was normal in 51% of patients with myocarditis. Nearly half of the patients with myocarditis experienced a major adverse cardiovascular event (MACE) defined as a composite of cardiovascular death, cardiogenic shock, cardiac arrest, or complete heart block.[5] Salem et al[6] also reported a 50% mortality rate with myocarditis. Other less common cardiac toxicities of immune checkpoint inhibitors include congestive heart failure or cardiomyopathy without proven myocarditis, pericardial disease, and conduction disease.[7]

Although myocarditis from immune checkpoint inhibitors is uncommon, the high mortality rate demands a high index of suspicion with expeditious diagnosis and management. Patients with such myocarditis present with a spectrum of disease severity, from asymptomatic troponin elevation or EKG changes to fulminant cardiogenic shock. Symptoms may include chest pain, shortness of breath, palpitations, or fatigue.[8] The diagnosis of immune-related myocarditis can be challenging due to lack of clear diagnostic criteria, and diagnostic methods are similar to those of myocarditis of other causes.[9] Troponin and natriuretic peptide levels are usually elevated and are recommended as initial assessment. EKG and telemetry can also be useful in the diagnosis and monitoring of intermittent arrhythmias such as ventricular tachycardia. Echocardiography can provide information on LVEF, wall motion abnormalities, and pericardial effusions and is used for diagnosis and assessment of treatment response. Cardiac magnetic resonance imaging (MRI) has the greatest ability to diagnose myocarditis noninvasively. Myocardial edema and non-ischemic injury on MRI are highly suggestive of myocarditis. The gold standard for diagnosis of myocarditis is endomyocardial biopsy, which can reveal inflammatory infiltrate and myocardial necrosis. But even an endomyocardial biopsy can miss the diagnosis due to focal involvement and sampling error.

Treatment of cardiac toxicity from immune checkpoint inhibitors includes withholding the offending agent and suppressing the immune response. Similar to treating other toxicities from immune checkpoint inhibitors, glucocorticoids are the mainstay of therapy. Prednisone 1-2 mg/kg or the IV steroid equivalent should be initiated urgently when the diagnosis is suspected and symptoms are present.[3] Due to the potential for morbidity and mortality, hospital admission and Cardiology consultation for assistance in management are generally recommended. Escalation of immunosuppression is warranted if there is no response to initial corticosteroids. Methylprednisolone 1 g IV daily along with either mycophenolate, infliximab, or antithymocyte globulin (ATG) may be beneficial, based on small case series.[8] Steroids can be tapered over 4 to 6 weeks, depending on response. Newer agents that have been used for treatment-resistant cases include abatacept (CTLA-4 agonist)[10] and alemtuzumab (anti-CD52 antibody).[11] Rechallenging patients who recover from immune-related cardiac toxicity with immune checkpoint inhibitors is generally not recommended due to the risk of recurrent life-threatening toxicity.

REFERENCES

1. **Siegel RL, Miller KD, Jemal A**. Cancer statistics, 2020. *CA Cancer J Clin*. 2020 Jan;70(1):7-30. doi: 10.3322/caac.21590. Epub 2020 Jan 8. PMID: 31912902.
2. **Havel JJ, Chowell D, Chan TA**. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. *Nat Rev Cancer*. 2019 Mar;19(3):133-150. doi: 10.1038/s41568-019-0116-x. PMID: 30755690; PMCID: PMC6705396.
3. **Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, Hallmeyer S, Chakrabarty JH, Leighl NB, Mammen JS, McDermott DF, Naing A, Nastoupil LJ, Phillips T, Porter LD, Puzanov I, Reichner CA, Santomasso BD, Siegel C, Spira A, Suarez-Almazor ME, Wang Y, Weber JS, Wolchok JD and Thompson JA in collaboration with the National Comprehensive Cancer Network**. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society

of Clinical Oncology Clinical Practice Guideline. *JCO*. 2018 Feb 14;36(17):1714–68.

4. **Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, Hicks M, Puzanov I, Alexander MR, Bloomer TL, Becker JR, Slosky DA, Phillips EJ, Pilkinton MA, Craig-Owens L, Kola N, Plautz G, Reshef DS, Deutsch JS, Deering RP, Olenchock BA, Lichtman AH, Roden DM, Seidman CE, Koralnik IJ, Seidman JG, Hoffman RD, Taube JM, Diaz LA Jr, Anders RA, Sosman JA, Moslehi JJ**. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. *N Engl J Med*. 2016 Nov 3;375(18):1749-1755. doi: 10.1056/NEJMoa1609214. PMID: 27806233; PMCID: PMC5247797.
5. **Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, Sullivan RJ, Damrongwatanasuk R, Chen CL, Gupta D, Kirchberger MC, Awadalla M, Hassan MZO, Moslehi JJ, Shah SP, Ganatra S, Thavendiranathan P, Lawrence DP, Groarke JD, Neilan TG**. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. *J Am Coll Cardiol*. 2018 Apr 24;71(16):1755-1764. doi: 10.1016/j.jacc.2018.02.037. Epub 2018 Mar 19. PMID: 29567210; PMCID: PMC6196725.
6. **Salem JE, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, Gobert A, Spano JP, Balko JM, Bonaca MP, Roden DM, Johnson DB, Moslehi JJ**. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol*. 2018 Dec;19(12): 1579-1589. doi: 10.1016/S1470-2045(18) 30608-9. Epub 2018 Nov 12. PMID: 30442497; PMCID: PMC6287923.
7. **Mir H, Alhussein M, Alrashidi S, Alzayer H, Alshatti A, Valettas N, Mukherjee SD, Nair V, Leong DP**. Cardiac Complications Associated With Checkpoint Inhibition: A Systematic Review of the Literature in an Important Emerging Area. *Can J Cardiol*. 2018 Aug;34(8):1059-1068. doi: 10.1016/j.cjca.2018.03.012. Epub 2018 Mar 28. PMID: 29980467.
8. **Palaskas N, Lopez-Mattei J, Durand JB, Iliescu C, Deswal A**. Immune Checkpoint Inhibitor Myocarditis: Pathophysiological Characteristics, Diagnosis, and Treatment. *J Am Heart Assoc*. 2020 Jan 21;9(2):e013757. doi: 10.1161/JAHA.119.013757. Epub 2020 Jan 21. PMID: 31960755; PMCID: PMC7033840.
9. **Müller OJ, Spehlmann ME, Frey N**. Cardio-toxicity of checkpoint inhibitors. *J Thorac Dis*. 2018 Dec;10(Suppl 35):S4400-S4404. doi: 10.21037/jtd.2018.12.78. PMID: 30701107; PMCID: PMC6328389.
10. **Salem JE, Allenbach Y, Vozy A, Brechot N, Johnson DB, Moslehi JJ, Kerneis M**. Abatacept for Severe Immune Checkpoint Inhibitor-Associated Myocarditis. *N Engl J Med*. 2019 Jun 13;380(24):2377-2379. doi: 10.1056/NEJMc1901677. PMID: 31189043.
11. **Esfahani K, Buhlaiga N, Thébault P, Lapointe R, Johnson NA, Miller WH Jr**. Alemtuzumab for Immune-Related Myocarditis Due to PD-1 Therapy. *N Engl J Med*. 2019 Jun 13;380(24):2375-2376. doi: 10.1056/NEJMc 1903064. PMID: 31189042.