

Clinical Characteristics and Outcomes in Immune Checkpoint Inhibitor Therapy-Associated Myocarditis

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Abstract

Immune checkpoint inhibitor (ICI) therapy has played an important role in the treatment of several groups of cancers. Although a life prolonging treatment, many side effects have been shown with ICI therapy. This study looked at individual level clinical characteristics and outcomes with ICI therapy in patients who developed ICI-related myocarditis. A comprehensive review of the National Library of Medicine PubMed database was performed. Inclusion criteria were all studies that were composed of case reports and case series of individual patients undergoing ICI therapy that developed myocarditis. To appreciate individual patient level data, observational studies, clinical trials, systematic reviews, and meta-analyses were excluded. Our search yielded 333 results with 71 cases reviewed of ICI therapy-related myocarditis. The findings included an average age of 68 years, higher incidence in men, and pretreatment cardiac history of hypertension. Melanoma was the most prevalent malignancy with nivolumab being the most used ICI therapy. Heart failure was the most prevalent adverse event that was co-prevalent with myocarditis. Corticosteroid therapy alone was the most utilized therapy to treat ICI-related myocarditis. Mortality was seen in nearly half of the patient population. Our study reviewed the preexisting literature of prior reported myocarditis secondary to ICI therapy. Periodic surveillance should be performed by the cardio-oncologist and internist. Due to the expanding role of ICI therapy in treating a variety of cancer pa-

tients, appreciation of its impact on the development of myocarditis is needed.

Keywords: Immune checkpoint inhibitor; Myocarditis; Heart failure; Cardio-oncology

Introduction

Immune checkpoint inhibitor (ICI) therapy has played an important role in the treatment of several groups of cancers. Through blockade of programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) immune checkpoints, this class of immunotherapies has been shown to even provide long-term remission [1]. Currently, seven ICI therapies exist that have been approved by the US Food and Drug Administration. These seven therapies treat a wide variety of malignancies and include ipilimumab approved in 2011, nivolumab approved in 2014, pembrolizumab approved in 2014, cemiplimab approved in 2018, avelumab approved in 2017, atezolizumab approved in 2016, and durvalumab approved in 2017. Although immune check point inhibitors have improved survival in many cancer patients, many side effects have been appreciated. In particular, myocarditis has been shown to be one of the deadliest. The mortality rate of ICI-associated myocarditis has been described as up to 50% with an incidence reaching an average of 0.5% [2]. This study looked at individual level clinical characteristics and outcomes with ICI therapy in patients who developed ICI-related myocarditis.

Methods

A comprehensive review of the National Library of Medicine PubMed database was performed. Keywords included in the search were “immune checkpoint inhibitor” and “myocarditis.” Database results were confirmed by multiple authors (RAT and MAL). Inclusion criteria were all studies that were composed of case reports and case series of individual patients undergoing ICI therapy that developed myocarditis to assess individual patient level data. Exclusion criteria for this review were case reports and case series where myocarditis was

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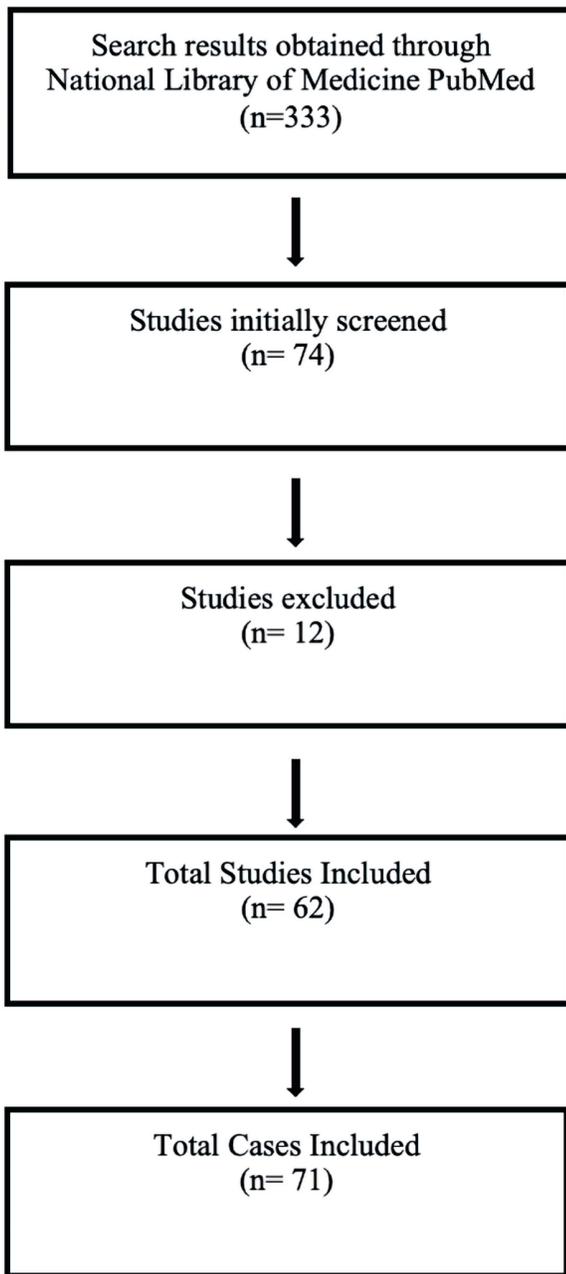


Figure 1. Case selection.

not one of the main immune therapy-related adverse events. Observational studies, clinical trials, systematic reviews, and meta-analyses were excluded due to difficulty assessing individual patient level data. Systematic analyses were not performed due to variability in data.

Results

Our search yielded 333 results with 71 cases reviewed of ICI therapy-related myocarditis (Fig. 1). The average age of the

Table 1. Patient Characteristics

	N	%
Gender		
Male	46	64.8%
Female	24	33.8%
No gender provided	1	1.4%
Pretreatment cardiovascular diagnosis		
Atrial fibrillation/atrial flutter	1	4.8%
History of arrhythmia	2	9.5%
History of coronary artery bypass grafting	2	9.5%
History of valve repair	1	4.8%
Hyperlipidemia	6	28.6%
Hypertension	19	90.5%
Myocardial infarction	1	4.8%
Peripheral artery disease	2	9.5%
Not provided/not applicable	50	
Malignancy		
> 1 malignancy	2	2.8%
Clear cell renal cell carcinoma (ccRCC)	2	2.8%
Chronic myelomonocytic leukemia (CMML)	1	1.4%
Glioblastoma	1	1.4%
Head and neck squamous cell carcinoma	3	4.2%
Hepatocellular carcinoma (HCC)	1	1.4%
Large cell neuroendocrine carcinoma (LCNEC)	1	1.4%
Lymphoma	1	1.4%
Melanoma	24	33.8%
Mesothelioma	3	4.2%
Non-small cell lung carcinoma (NSCLC)	18	25.4%
Periocular squamous cell carcinoma	1	1.4%
Prostate adenocarcinoma	2	2.8%
Renal cell carcinoma (RCC)	5	7.0%
Sarcoma-alveolar soft part	1	1.4%
Serous endometrial carcinoma	1	1.4%
Thymic cancer	1	1.4%
Thymoma	1	1.4%
Urothelial cancer	2	2.8%

patient population was 68 years. Males accounted for most cases at 64.8%, while females accounted for 33.8%. Gender was not provided in one case. The most common pretreatment cardiovascular diagnosis that patients had was hypertension accounting for 90.5%. Hyperlipidemia was the second most common cardiac comorbidity at 28.6%. Prior cardiovascular diagnosis was either not reported or not applicable in 50 cases. The most common malignancy reported was melanoma at 33.8%. Non-small cell lung carcinoma (NSCLC) accounted for the second most reported malignancy at 25.4% (Table 1).

The most common ICI therapy reported was nivolumab accounting for 38% of cases. A combination of multiple ICI therapy was used in 28.2% of cases. The most common adverse event seen with co-prevalent myocarditis was heart failure in 38.5% of cases. The second most co-prevalent adverse event was heart block seen in 27.7% of cases. Adverse events were not reported in six cases. Treatment with corticosteroid therapy alone for ICI-associated myocarditis accounted for 56.3% of cases. Any combination of therapies including plasma exchange or plasmapheresis was seen in 11.3% of cases. Therapy was either not stated or unknown in two cases. Death was seen in 49.3% of cases. One case did not report mortality outcomes (Tables 2, 3) [3-64].

Discussion

Our study reviewed the preexisting literature of prior reported myocarditis secondary to ICI therapy. Although variability in data exists, individual patient level outcomes appreciated in our study were a higher incidence of ICI-associated myocarditis in males compared to females. This adverse effect was also seen mostly in patients around 68 years of age. Hypertension was the most common pretreatment cardiovascular diagnosis. Melanoma was the most prevalent malignancy, with nivolumab being the most used ICI therapy. Other notable outcomes included heart failure being the most prevalent adverse event that was co-prevalent with myocarditis. Corticosteroid therapy alone, with either methylprednisolone or prednisone, was the most utilized therapy to treat ICI-related myocarditis. Mortality was seen in nearly half of the patient population. There was notable higher incidence of mortality among patients on nivolumab 3 mg/kg compared to 2 mg/kg. One of the major limitations of our review was that in several of the cases prior medications, especially prior beta blocker use, were not mentioned [3-64].

Pathophysiology

Immunotherapy is a biological therapy, derived from living organisms that is used to treat cancer. While the immune system normally functions to destroy cancer cells, some cancers have found ways to avoid destruction [65]. The anti-PD-1 monoclonal antibodies (mAb) include nivolumab, pembrolizumab, and cemiplimab. These mAbs bind to PD-1 and prevent binding with PD-L1 and programmed death-ligand 2 (PD-L2) on the tumor surface. This allows for PD-1-associated immune response to act against tumor cells [66]. Pembrolizumab and cemiplimab are also anti-PD-1 mAbs; however, their differences lie in the variable regions in which antigen binding occurs. This explains the difference in indications between the drugs, despite their nearly identical mechanism [67, 68]. Like the anti-PD-1 agents, the anti-PD-L1 antibodies block PD-L1 on the tumor surface; these anti-PD-L1 therapies include avelumab, atezolizumab, and durvalumab [69].

Ipilimumab, the first FDA-approved ICI, is a mAb that binds to CTLA-4 and blocks interaction with its ligands CD80

(B7-1) and CD86 (B7-2). Through this inhibition of CTLA-4 signaling, regulatory T-cell function is reduced, leading to increased T-cell and anti-tumor immune responses [70, 71]. Combination therapy with nivolumab (anti-PD-1 mAb) and ipilimumab (anti-CTLA-4 mAb) is currently used in many different cancers, leading to greater response rates and overall survival. On the contrary, these advances come with more immune-related adverse effects [72]. ICI-associated myocarditis has been noted as being a seemingly rare immune-related adverse effect in prior literature, although reporting of this adverse effect has grown over time [73].

Currently, there is no accepted mechanism for which this occurs; however, several suggested mechanisms exist. One proposed mechanism of ICI-associated myocarditis is through T cell infiltration. Johnson et al reported two cases of lethal myocarditis in combination with myositis in patients receiving nivolumab in combination with ipilimumab [74]. In their study, post-mortem cardiac histopathology showed T-cell infiltration with CD4 and CD8 positivity. It was also found that the patients shared high-frequency T-cell receptor sequences in the skeletal and cardiac muscle as well as tumor cells. Through these interactions, the authors propose that T cells target a shared antigen on the tumor, cardiac myocytes, and skeletal muscle which leads to cellular injury. Another similar mechanism discussed is T-cell receptors targeting tumor antigens and different yet similar muscle antigen. Finally, they propose that high-frequency T-cell receptors in both muscle and tumor cells deceive T-cells into targeting the wrong antigen [74].

In studies on mice, PDL-1 was found to be cardioprotective against T-cell-associated injury [74, 75], and mice deficient in the programmed cell death-1 immunoinhibitory co-receptor developed autoimmune dilated cardiomyopathy due to autoantibodies against troponin I [76]. CTLA-4, the target of ipilimumab, has been shown to have a role in T-cell activation. Tivol et al demonstrated that CTLA-4 deficient mice developed myocarditis leading to death within 3 - 4 weeks of life, showing the negative role and cardioprotective effect of CTLA-4 [77]. When CTLA-4 is used as an ICI, the anti-CTLA-4 antibody interferes with CTLA-4 and B7-1, effectively lowering the activation threshold of cardiac reactive T cells [78]. Therefore, oncologic treatments using ICIs causing blockade of PD-1, PDL-1, and CTLA-4 have been implicated in promoting cardiac myocyte injury [79].

Diagnostic considerations in ICI-associated myocarditis

Diagnosis of ICI-related myocarditis involves obtaining a comprehensive cardiac profile. Review of systems will usually be positive for symptoms such as angina, dyspnea, orthopnea, and lower extremity edema. Physical examination findings may include development of a S3 gallop, jugular venous distention, lower extremity pitting edema, tachycardia, and hypotension with cardiogenic shock. Pertinent laboratory markers include obtaining troponin and brain natriuretic peptide (BNP) which may be abnormal. Electrocardiogram can also be helpful in assessing for arrhythmias, although at times may be normal [80]. The initial imaging modality should be echocardiogram with close assessment of global longitudinal strain and

Table 2. Patient Outcomes

	N	%
ICI therapy		
Atezolizumab	1	1.4%
Cemiplimab	1	1.4%
Durvalumab	1	1.4%
Ipilimumab	1	1.4%
Multiple immune checkpoint inhibitors used	20	28.2%
Nivolumab	27	38.0%
Pembrolizumab	19	26.8%
Sintilimab	1	1.4%
Adverse events with coprevalent myocarditis		
Acute kidney injury	6	9.2%
Acute liver injury	12	18.5%
Acute respiratory failure	5	7.7%
Adrenal insufficiency	1	1.5%
Arrhythmias	12	18.5%
Atrial fibrillation	5	7.7%
Autoimmune diabetes mellitus	1	1.5%
Colitis	3	4.6%
Encephalitis	1	1.5%
Heart block	18	27.7%
Heart failure	25	38.5%
Hypophysitis	1	1.5%
Myasthenia gravis/crisis	14	21.5%
Myositis	16	24.6%
Pericardial effusion	1	1.5%
Pneumonitis	5	7.7%
Rhabdomyositis	1	1.5%
Thyroiditis	2	3.1%
Not reported	6	
Treatment		
Corticosteroid therapy alone	40	56.3%
Intravenous immunoglobulin (IVIG) alone	1	1.4%
Anti-thymocyte globulin (ATG) alone	0	0.0%
Supportive care	1	1.4%
Corticosteroid + immunosuppressant (tacrolimus, mycophenolate mofetil)	3	4.2%
Corticosteroid + IVIG	6	8.5%
Corticosteroid + IVIG + immunosuppressant	1	1.4%
Not stated/no treatment	2	2.8%
Corticosteroid + ATG	2	2.8%
Corticosteroid + tofacitinib	1	1.4%
Corticosteroid + IVIG + tofacitinib	1	1.4%
Corticosteroid + infliximab	3	4.2%
Corticosteroid + IVIG + infliximab	1	1.4%
Corticosteroid + immunosuppressant + ATG + infliximab	1	1.4%
Any combination including plasma exchange/plasmapheresis	8	11.3%
Mortality		
Alive	35	49.3%
Death	35	49.3%
Unknown	1	

Table 3. Associated Mortality

	Mortality number	Mortality (%)
Gender		
Male	24/46	52.2%
Female	9/24	37.5%
ICI therapy		
Atezolizumab	1/1	100%
Cemiplimab	1/1	100%
Durvalumab	0/1	0%
Ipilimumab	0/1	0%
Nivolumab	14/27	51.9%
Pembrolizumab	7/19	36.8%
Multiple immune checkpoint inhibitors	10/20	50%
Associated adverse events by highest incidence		
Heart failure	11/25	44%
Heart block	12/18	66.7%
Myositis	11/16	68.8%
Myasthenia gravis/crisis	5/14	35.7%
Arrhythmias	6/12	50.0%
Acute liver injury	7/12	58.3%
Acute kidney injury	4/6	66.7%

left ventricular ejection fraction. Cardiac magnetic resonance imaging has also been noted as being helpful in evaluation of the myocardium in ICI-associated myocarditis but with overall poor sensitivity. Ultimately, the main determining diagnostic modality is endomyocardial biopsy [81]. Endomyocardial biopsy usually demonstrates a predominance of lymphocytes with myocyte necrosis along with fibrosis and inflammation [82]. Global longitudinal strain has recently become an area of interest in assessing the degree of cardiac insult in patients who develop ICI-associated cardiotoxicity. In an international retrospective study, 101 cases of myocarditis in patients undergoing ICI therapy were evaluated. Notable findings from this large study were that global longitudinal strain was decreased in patients who developed myocarditis, with this decrease found in patients with both reduced and preserved ejection fractions. Furthermore, there was correlation between major adverse cardiovascular events in patients with low global longitudinal strain and myocarditis [83].

Treatment modalities for ICI-associated myocarditis

Although, no definitive treatment protocols exist, guidelines for the treatment of ICI-related myocarditis have been developed by the American Society of Clinical Oncology. For patients presenting with grade 1 chemotoxicity, which is elevation of biomarkers in the absence of symptoms or higher, ICI therapy should be stopped and discontinued permanently. High-dose prednisone at 1 - 2 mg/kg should be administered promptly.

Patients who do not respond to high-dose prednisone should be trialed on methylprednisolone 1 g every day in combination with immunosuppressive therapy such as mycophenolate mofetil, infliximab, or antithymocyte globulin until resolution of myocarditis [84]. In patients with New York Heart Association class III or IV heart failure, the use of infliximab is relatively contraindicated. For this subclass of patients with heart failure and ICI-related myocarditis, the use of antithymocyte globulin or tacrolimus in combination with high-dose steroids has been shown to be more appropriate [85].

Conclusions

As demonstrated in our review, the understanding of the mechanisms underlying ICI-associated myocarditis is still ongoing. Furthermore, patients may present asymptotically or in cardiogenic shock. Prior to initiation of therapy, a baseline cardiac profile including biomarkers such as troponin and BNP should be obtained in conjunction with a baseline echocardiogram. Periodic surveillance should be performed by the cardio-oncologist and internist. Due to the expanding role of ICI therapy in treating a variety of cancer patients, further appreciation of its impact on the development of myocarditis is needed.

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None to declare.

Conflict of Interest

The authors declare that they do not have a conflict of interest.

Author Contributions

All authors had access to the data and a role in writing the manuscript. RAT: conceptualization, data curation, writing of draft preparation, reviewing, and editing. MAL: data curation, writing of draft preparation, reviewing, and editing. AA, AE, KHS, and CP: writing of reviewing and editing. LKS, NMF, RV, WK, RFB, and KFC: writing of reviewing and editing, expert opinion.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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