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Cardiac Toxicities of Immune Checkpoint Inhibitors: More Awareness is Needed

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ABSTRACT

Immune checkpoints inhibitors (ipilimumab, nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab, durvalumab) are monoclonal antibodies that target cell membrane receptors (CTLA-4, PD-1, PDL-1) implicated in the immunosuppression. This results in activation of the lymphocytic immune response leading to CD8+ T cells proliferation in many organs including the heart. However, the management consists of stopping the immunotherapy and starting high-dose corticosteroids. The incidence of these toxicities as well as their pathophysiology, risk factors, onset and prognosis are not clearly established yet due to the lack of data and cohort studies. Despite the FDA approval of these drugs in the treatment of many refractory cancers, they should be used with caution due to their devastating repercussions.

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Abbreviations

CVAEs: Cardiovascular Adverse Events
CTLA-4: Cytotoxic T Lymphocyte Antigen 4
EKG: Electrocardiogram
ICIs: Immune Checkpoint Inhibitors (ICIs)
IRAEs: Immunological-Related Adverse Effects
IVIG: Intravenous Immunoglobulins
PD-1: Programmed Cell Death 1
PD-L1: Program Death Receptor Ligand 1

Introduction

Besides the conventional methods, immune checkpoint therapy has opened up several avenues of hope in cancer treatment [1]. In the immune system, a combination of co-stimulation and inhibitory pathways modulates T cell activation. Ligands expressed by antigen-presenting cells can bind to co-inhibition pathway receptors on T cells, such as Cytotoxic T cell Lymphocyte-Associated Protein 4 (CTLA-4) or programmed death receptor 1 (PD-1) receptors. Subsequently, T cells' immunological response and cell proliferation are decreased. In order to evade the local immune response that would lead to their programmed death, tumor cells over-express these ligands, resulting in uncontrolled growth [2-5].

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that function as receptor antagonists, reawakening native T cells' anticancer response. To ascertain the activation of T cells and subsequent tumor control, many antibodies have been developed to target cellular immunological checkpoints, including PD-1, program death receptor ligand 1(PD-L1), and CTLA-4, in order to activate T cells and subsequently control tumors (Shown in Figure: 1) [6].

It's crucial to comprehend how ICIs function to predict their potential toxicities. Since immune checkpoints play a vital role in preventing self-destruction, blocking them can trigger immune-related side effects (IRAEs). While any organ system can be affected by IRAEs, the digestive, hormonal, respiratory, and nervous systems are particularly susceptible. These side effects can sometimes be mild, making them hard for healthcare professionals to detect [7].

Cardiovascular Adverse Events (CVAEs), though uncommon, are being reported more and more because of the widespread usage of ICIs. Recent retrospective studies have shown that CVAEs with ICIs may include pericarditis, vasculitis, myocarditis, and heart failure as well as potentially lethal arrhythmias [8]. Recent studies hypothesized that a plausible explanation could involve the significant proliferation and clonal expansion of T lymphocytes with a high-frequency T-cell receptor against shared common antigens in tumor cells and afflicted organs [9].

The purpose of this review is to elaborate the incidence, onset, and prevalence of the different ICI's cardiotoxicities, followed by the clinical manifestations of each toxicity with its diagnostic techniques, the summary of the overall management, and finally the prognosis and prevention.

Immune Checkpoint Inhibitors

Immune checkpoints are PD-1, PD-L1 and CTLA-4. These cell membrane receptors downregulate the immune response. In the tumor environment, their upregulation is one of the reasons behind the tumor's survival. ICIs are antibodies such as Ipilimumab (anti CTLA-4), nivolumab, pembrolizumab and cemiplimab (anti PD-1), atezolizumab, avelumab and durvalumab (anti PD-L1)), that target these receptors, thus activate T cells and boost the antitumor immune activity [10-12].

In fact, the binding between B7 (a type of integral membrane protein found on antigen presenting cells, mainly in lymphoid tissues) and CD28 (on T cells), as well as the presentation of the tumor antigen to CD8+ T cytotoxic cells, are needed for T cells' activation, proliferation, and secretion of cytolytic molecules. This leads to tumor cell's death. The interaction between PD-L1 (expressed on tumor and immune cells in peripheral tissues) and PD-1 (on activated T effector cells), combined with the CD28/CTLA-4's B7-binding competition, plays a role in immunosuppression and tumor's evading system. CTLA-4 also plays a role in the maintenance of CD4+ regulatory T cells' suppression activity [13-16]. (Shown in Figure:1).

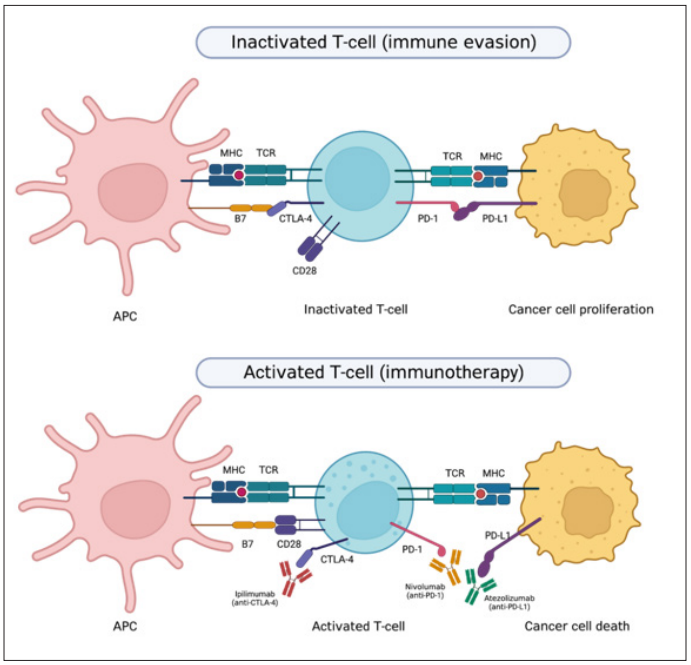

Figure 1: Mechanism of Action of ICIs

Cardiotoxicity of ICIs: Definition, Incidence, Onset, and Prevalence

The explanation behind ICI toxicities relies upon the hyperactivation of T cells, targeting both tumor and normal cells. A recent study has confirmed the presence of cytotoxic CD8+ T cytotoxic cells in cardiomyocytes during ICI treatment, with PD-L1 widely expressed on myocardial cells' surface, leading to the hypothesis that cardiac and tumor cells may have antigens in common, and are recognized by the same clone of T-cells. The resulting autoimmunity and lymphocytic infiltration can affect many organs including the heart [15,17]. (Shown in Figure: 2).

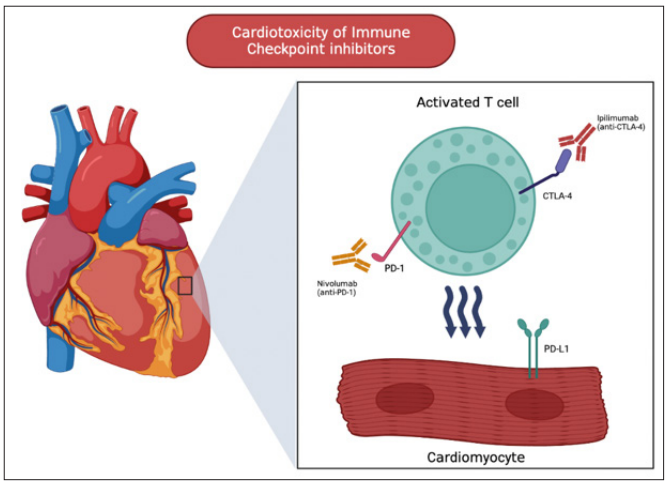

Figure 2: Mechanism of cardiotoxicity induced by ICIs

The real number of ICI-induced cardiovascular events is undervalued due to the lack of studies related to this topic [18]. Compared to others, cardiac toxicities induced by immune checkpoint inhibitors are rare but severe, and their incidence varies from 0.06% to 2.4% [19]. Manifestations can appear in less than three months after administration. Fulminant cases may occur even after the first few doses, and combination therapy worsens the prognosis [20-22].

The risk factors of ICI-induced cardiac toxicities remain unclear. Toxicities are more prevalent in patients who have cardiovascular risk factors, coexistent or preexistent cardiac diseases, underlying auto-immune pathologies, other immunotherapy-induced diseases, patients who have been exposed to cardiotoxic agents (anthracyclines, chest radiotherapy) or to combined immunotherapy agents [23]. Even if women are more predisposed to autoimmune events, the higher frequency of cardiovascular diseases in men and their better response to ICI, may explain why both sexes are not equally affected by ICI adverse effects [23,24].

Clinical Manifestations and Diagnosis

According to American Society of Clinical Oncology guidelines, ICI-induced adverse events can be divided into 4 grades of severity (Shown in Table: 1) [25-27].

Table 1: Grades of severity of ICI-induced cardiotoxicities

	Screening tests (EKG, cardiac biomarkers, echocardiogram)	Symptoms
Grade 1	Abnormal	None
Grade 2	Abnormal	Mild
Grade 3	Abnormal	Moderate to severe
Grade 4	Abnormal	Life-threatening

Myocarditis

Myocarditis is the most common clinical cardiac adverse event with an incidence rate that varies between 0.04% and 1.14%, a high fatality rate of 25% to 50%, a median time to onset of 4 weeks, depending on the treatment (anti-CTLA-4 versus anti-PD-1 versus anti-PD-L1 versus combination therapy) [4,28,29]. The combination of anti PD-1 or anti PD-L1 with anti CTLA-4 seems to increase the incidence of myocarditis by a factor of 4 compared with monotherapy, as well as the fatality rate that exceeds 60% [21,25,29]. This combination therapy also reduces the time to

onset of symptoms (median onset of 17-34 days) [20,30]. ICI-induced CVAEs are more frequent with CTLA-4 antibodies administration [6,31-33]. This can be explained by the differences in the mechanism of action between PD-1 and CTLA-4. The latter plays a role in the primary stage of immune response and has a wider spectrum of action [16]. In fact, a meta-analysis that aimed to compare the immune related adverse events of ICI showed that Ipilimumab has the highest incidence (82.12%), followed by nivolumab (76.25%), atezolizumab (68.77%), pembrolizumab (67.25%), durvalumab (66.63%) and finally avelumab (44.53%), which shows that ICI-induced adverse events are more prominent with CTLA-4 blockers (82.87%) [24,33].

Pericardial disease, Takotsubo cardiomyopathy, myocardial infarction, vasculitis, supraventricular or ventricular tachyarrhythmias, and conduction abnormalities have also been reported with lower prevalence as compared to myocarditis [24,33,34]. In a pharmacovigilance study that evaluated the CVAEs, pericardial diseases appear to be more prominent in patients with lung cancer, while myocarditis and vasculitis are mostly found in patients with melanoma [35].

The severity and course of myocarditis are variable, ranging from mild, asymptomatic cases, to life threatening manifestations. There are no typical clinical findings. Fatigue, myalgia, dyspnea, heart failure (Pulmonary Edema), palpitations, syncope, chest pain, hypotension (Cardiogenic Shock), altered mental status, cardiac arrest are possible presentations [23]. Myocarditis should be suspected in patients with or without cardiac symptoms in the presence of new electrocardiogram changes suggestive of cardiac injury, arrhythmia or ventricular systolic dysfunction associated with a rise in cardiac biomarkers in the absence of an acute coronary syndrome. Ischemic evaluation can be indicated in selected patients to rule out a coronary etiology. Cardiovascular magnetic resonance can detect edema and scarring, as well as ventricular size and function. It is therefore highly sensitive and specific for myocarditis in general but its role in ICI-mediated cardiotoxicity remains debatable [10].

A definitive diagnosis of myocarditis can be made upon endomyocardial biopsy. However, due to the invasive nature of this procedure, and since it does not significantly impact the patient's management, its clinical value is debatable. If pursued, endomyocardial biopsy in patients with ICI-mediated myocarditis typically shows CD8+ T-cells, CD68+ macrophages and signs of myocardial fibrosis. Lymphocytic infiltration seen in the sinoatrial and atrioventricular nodes could explain the ICI-related conduction abnormalities [34].

Pericarditis

Pericarditis can occur in isolation without myocardial injury, or in association with myocarditis where cardiac enzymes would be significantly elevated. Symptoms of pericardial involvement are non-specific, typically including pericardial pain. Shortness of breath, venous congestion and signs of cardiogenic shock can be reported in association with pericardial effusion [36]. The electrocardiogram (EKG) is typically altered: diffuse ST elevation, inverted T waves low QRS voltage, tachycardia and electrical alternans can be seen in the presence of cardiac tamponade [3,25].

Transthoracic echocardiography can be normal in isolated pericarditis but is a sensitive test for the detection and quantification of associated pericardial effusions by identifying cardiac tamponade or constrictive pericarditis and can also guide a diagnostic or therapeutic perdicardiocenstesis. If pericardial fluid is retreived, cytologic analysis typically shows lymphocytosis and absence of tumoral cells [37].

The cardiovascular magnetic resonance can help identify pericardial inflammation as well as concomitant myocardial inflammation or fibrosis [25]. Moreover, it can identify a subgroup of patients with subacute inflammatory constrictive pericarditis who may still respond to anti-inflammatory therapy [38].

Arrhythmias

ICIs have been associated with various types of arrhythmias. The most described tachyarrhythmia is atrial fibrillation, followed by ventricular tachycardia or ventricular fibrillation. Bradyarrhythmia, secondary to conduction disease and heart block, can also described and are associated with increased cardiovascular mortality in patients receiving ICIs. Conduction abnormalities can be observed in the setting of ICI-related myocarditis but can also occur in isolation [23,24,37].

A report of patchy lymphocytic infiltration into the sinoatrial and atrioventricular nodes suggests that ICI-associated conduction disease could be related to T-cell-mediated cytotoxicity [37,39].

Screening for palpitations, near syncope or syncope as well as careful EKG and heart rhythm monitoring can help with the early recognition and management of those potentially life-threatening arrhythmias [35,37].

Other Cardiovascular Adverse Events

Other cardiovascular adverse events (Increase in Blood Pressure, Takotsubo Syndrome, Myocardial Infarction) have also been reported but to a lesser extent. The mechanistic association between ICIs and Takotsubo syndrome remains unclear. Proposed mechanisms include an indirect effect secondary to the abrupt release of large amounts of catecholamines causing myocardial stunning or a more direct effect of ICI causing coronary vasospasm (34).

Takotsubo cardiomyopathy is diagnosed by cardiac imaging that shows transient regional wall motion abnormality, associated with new EKG abnormalities or modest troponin elevation, in the absence of coronary obstruction or myocarditis [34,36,37].

Management

According to American Society of Clinical Oncology, the Society for Immunotherapy of Cancer, the European Society for Medical Oncology and the National Comprehensive Cancer Network guidelines, in case of CVAEs following immunotherapy, the management should not be delayed [18-40].

In all cases, admit patient, monitor closely, consult a cardiologist, transfer to the Cardiac Care Unit in case of troponins and conduction changes, control cardiovascular comorbidities, stop ICI (permanently for grades 2 to 4) and treat heart failure and arrhythmia according to the American College of Cardiology and the American Heart Association guidelines.

The grade 2 to 4 therapeutic approach is well described in the following escalating process (Shown in Figure: 3).

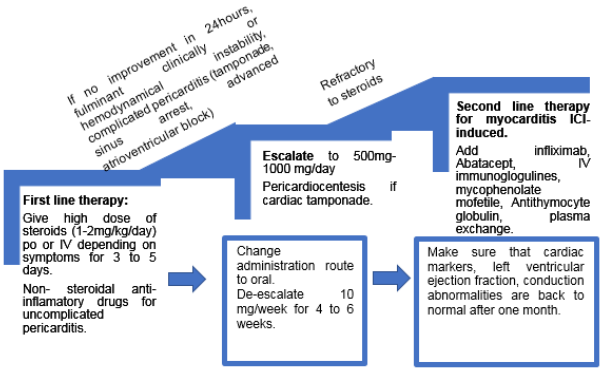

Figure 3: Management of ICI-induced cardiotoxicities

First line therapy consists of high dose of steroids during 3 to 5 days. In case of improvement, the next step is to deescalate and slowly decrease the dose until the disappearance of symptoms.

In case of aggravation, pulse therapy should be given. For refractory cases, second line therapy of immunosuppressors is the last attempt (mycophenolate, infliximab, antithymocyte globulin (ATG), or abatacept). The aim of these agents is to reduce the inflammation.

ATG acts as an antibody against T cells receptors implicated in T cells activation process, thus leading to downregulation of CD3+ cells in a short delay of time (24 hours). Its use is not without harmful consequences as it may lead to cytopenia, fever and chills [25,41].

Infliximab inhibits Tumor necrosis factor-alpha (a cytokine implicated in the inflammatory process). It has been efficient in myocarditis refractory to corticosteroids. Its use is not recommended in patients with moderate to severe heart failure [25].

Abatacept, a CTLA-4 agonist, has been of great benefit in treating heart failure, ventricular arrhythmia, and high troponin level after severe cases of myocarditis. Its mechanism of action relays on the inactivation of the T cell co-stimulation pathway (CD28-B7), which can result in depression of the normal immunologic response [25,42].

Plasma exchange gets rid of immunoglobulins. Its use is encouraged in refractory to steroids cases [30].

Intravenous Immunoglobulins (IVIG) aim to inhibit cytokines and T-cell activation through antigen presentation cells downregulation [43].

The mechanism of action, indication and adverse events of these agents are summarized in Table 2.

Table 2: Second-line therapy's main characteristics of ICI-induced cardiotoxicities

Molecule	Mechanism of action	Indication	Adverse events
ATG	Complement-dependent lysis leading to T cells depletion	Unstable patients	Cytopenia, fever, chills
Infliximab	TNF alpha inhibition	Stable myocarditis refractory to corticosteroids	Heart failure exacerbation
Abatacept	CTLA-4 agonist	Severe cases with heart failure and arrhythmia	T cells anergy
Plasma exchange	Immunoglobulins depletion	Unstable patients	Flu-like symptoms, increase in blood pressure, tachycardia
IVIG	Cytokines and T cells inhibition	Unstable patients	Flu-like symptoms, increase in blood pressure, tachycardia

ATG, antithymocyte globulin; TNF, tumor necrosis factor; IVIG, intravenous immunoglobulins; CTLA-4, cytotoxic T-lymphocyte-associated protein 4

Screening, Prognosis, and Future Perspectives

For ICI-induced moderate to severe myocarditis and for life-threatening complications, re-challenging of ICI with cardiac monitoring is not recommended, unlike in resolved pericarditis [26,36]. The importance of screening and cardiac surveillance during ICI administration is not established yet. Because of the lack of data, more studies should be done to better understand, evaluate and treat these relatively rare complications of ICI-cardiotoxicities [3,24].

Conclusion

ICI have proven their efficiency in many metastatic cancers that are refractory to traditional treatments. Their use is primordial. However, there has been subsequent intolerable and even life-threatening ICI-induced adverse events targeting many organs, which have reduced their clinical use. The management should be started without any delay with high-dose corticosteroids as the mainstay of therapy and it includes, in most of the cases, the permanent discontinuation of ICI. The real incidence and prevalence of cardiotoxicities is underestimated due to lack of large studies related to this topic with the bulk of the data originating from case reports. The cardiac complications are relatively rare but may be fatal especially with myocarditis that has a poor prognosis, and therefore more awareness is needed to better screen for the adverse events, evaluate the prognosis and initiate the treatment as soon as possible.

Practice Points

- ICIs (Ipilimumab, Nivolumab, Pembrolizumab, Cemiplimab, Atezolizumab, Avelumab, Durvalumab) are monoclonal antibodies that target cell membrane receptors (CTLA-4, PD-1, PDL-1) implicated in the immunosuppression, which results in T CD8+ cytotoxic proliferation in many organs.
- Compared to others, cardiac toxicities induced by ICIs are rare but severe, their incidence varies from 0.06% to 2.4%, manifestations can appear in less than three months after administration and combination therapy worsens the prognosis.
- Myocarditis is the most common symptom of ICI induced cardiotoxicities with high risk of fatality; the severity and course of myocarditis are variable ranging from mild asymptomatic cases to life threatening manifestations.
- A definitive diagnosis of myocarditis can be made upon endomyocardial biopsy which shows CD8+ T-cells, CD68+ macrophages and signs of myocardial fibrosis, however the invasive nature of this intervention, reduces its clinical value.
- Pericarditis can occur in isolation without myocardial injury, or in association with myocarditis, it can have a constrictive pattern and may also lead to cardiac tamponade in some cases.
- ICIs have been associated with various types of arrhythmias that can be related to lymphocytic infiltration of the sinoatrial and atrioventricular nodes leading to conduction abnormalities.
- The management of ICI induced cardiotoxicities should be started without any delay with high-dose corticosteroids as the mainstay of therapy and it includes in most of the cases, the permanent discontinuation of ICI.
- For refractory to steroids cases, second line therapy of immunosuppressors (mycophenolate, infliximab, ATG, or abatacept) is the last attempt and their aim is to downregulate the immune system activation, the CD8+ T cytotoxic cells proliferation and to reduce the inflammation.
- More awareness is needed to better screen for the adverse events, evaluate the prognosis and initiate the treatment as soon as possible.

Author Contributions

Authors Jad Nicolas and Jessica Nicolas were responsible for the literature review, manuscript writing, and editing. Both authors reviewed the manuscript before submission.

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Disclosures

The authors declare that they have no conflict of interest related to this publication.

References

1. Zhang H, Chen J (2018) Current status and future directions of cancer immunotherapy. J Cancer 9: 1773-1781.
2. Hu JR, Florido R, Lipson EJ, Naidoo J, Ardehali R, et al. (2019) Cardiovascular toxicities associated with immune checkpoint inhibitors. Cardiovascular Research 115: 854-868.
3. Tajiri K, Ieda M (2019) Cardiac Complications in Immune Checkpoint Inhibition Therapy. Front Cardiovasc Med 6: 3.
4. Khunger A, Battel L, Wadhawan A, More A, Kapoor A, et al. (2020) New Insights into Mechanisms of Immune Checkpoint Inhibitor-Induced Cardiovascular Toxicity. Curr Oncol 22: 65.
5. Lyon AR, Yousaf N, Battisti NML, Moslehi J (2018) Immune checkpoint inhibitors and cardiovascular toxicity. The Lancet Oncology 19: 447-458.
6. Heinzerling L, Ott PA, Hodi FS, Husain AN, Tajmir-Riahi A, et al. (2016) Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. j immunotherapy cancer 4: 50.
7. Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, et al. (2016) Immune-related adverse events with immune checkpoint blockade: a comprehensive review. European Journal of Cancer 54: 139-148.
8. Dubin K, Callahan MK, Ren B, Khanin R, Viale A, et al. (2016) Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nat Commun 7: 10391.
9. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, et al. (2016) Fulminant Myocarditis with Combination Immune Checkpoint Blockade. N Engl J Med 375: 1749-1755.
10. Park R, Winnicki M, Liu E, CHU WM (2019) Immune checkpoints and cancer in the immunogenomics era. Briefings in Functional Genomics 18: 133-139.
11. Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, et al. (2017) PD-1 and PD-L1 Checkpoint Signaling Inhibition for Cancer Immunotherapy: Mechanism, Combinations, and Clinical Outcome. Front Pharmacol 8: 561.
12. Waliany S, Lee D, Witteles RM, Neal JW, Nguyen P, et al. (2021) Immune Checkpoint Inhibitor Cardiotoxicity: Understanding Basic Mechanisms and Clinical Characteristics and Finding a Cure. Annu Rev Pharmacol Toxicol 61: 113-134.
13. Ma W, Gilligan BM, Yuan J, Li T (2016) Current status and perspectives in translational biomarker research for PD-1/PD-L1 immune checkpoint blockade therapy. J Hematol Oncol 9: 47.
14. Borcherding N, Kolb R, Gullicksrud J, Vikas P, Zhu Y, et al. (2018) Keeping Tumors in Check: A Mechanistic Review of Clinical Response and Resistance to Immune Checkpoint Blockade in Cancer. J Mol Biol 430: 2014-2029.
15. Varricchi Gilda, Galdiero Maria Rosaria, Tocchetti Carlo G (2017) Cardiac Toxicity of Immune Checkpoint Inhibitors. Circulation 136: 1989-1992.
16. Buchbinder EI, Desai A (2020) CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. American Journal of Clinical Oncology 39: 98-106.
17. Kennedy LB, Salama AKS (2020) A review of cancer immunotherapy toxicity. CA A Cancer J Clin 70: 86-104.
18. Zhang L, Jones-O'Connor M, Awadalla M, Zlotoff DA, Thavendiranathan P, et al. (2019) Cardiotoxicity of Immune Checkpoint Inhibitors. Curr Treat Options Cardio Med 21: 32.