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Cardiac Immune Related Adverse Events in Immune Checkpoint Inhibition Therapy

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ABSTRACT

Immune checkpoint inhibitors present clinicians with both an exciting step forward in cancer treatment and the unknown possibilities of an unshackled immune system. The latter phenomena, known as immune-related adverse events (irAEs), are of particular interest because they may affect any organ system with autoimmune-like pathologies, such as hepatitis and colitis. Within the cardiovascular system, irAEs associated with immune checkpoint blockade exist as a broad clinical spectrum, with autoimmune myocarditis being the best-characterized entity at this time. In general, irAEs are often reversible with immunosuppression. However, irAEs which affect the cardiovascular system pose the possibility of a rapid and fatal clinical deterioration. The mortality attributed to immune checkpoint blockade-associated autoimmune myocarditis, as reported in the WHO database, exists from 36-67%, dependent on the therapeutic regimen. Yet, despite the potential severity such events pose, guidelines dictating the identification of immune checkpoint inhibition irAEs do not exist, providing a stark contrast with other anti-cancer medications with known cardiovascular effects. The lack of guidelines may be related to the perceived rarity of these events; yet a recent study of immune checkpoint inhibition-associated autoimmune myocarditis suggests this clinical entity may be more prevalent than initially believed. Until more standardized information regarding these potentially serious events is available, the study of documented cases is instructive to improve identification of such phenomena, as well as the outcomes for patients who develop them.

Keywords: Cardiotoxicity, Immune Checkpoint Blockade, Myocarditis, Autoimmune, Cardio-Oncology
In recent years, the development of immune checkpoint inhibitors such as ipilimumab, nivolumab, and pembrolizumab have provided hope for patients diagnosed with malignancies having previously dismal prognoses, such as metastatic melanoma.\textsuperscript{1} Historically, the standard of care for such malignancies included systemic cytotoxic medications such as dacarbazine or temozolomide, which offered limited efficacy and caused harsh systemic side effects.\textsuperscript{2, 3} As a result, many patients with pre-existing organ dysfunction could not tolerate the side effects accompanying optimal chemotherapeutic regimens.\textsuperscript{4} The development of immune checkpoint inhibitors to treat such malignancies has not only provided a source of optimism by offering patients response rates as high as 40% and remarkable survival data, but have also offered very tolerable safety profiles.\textsuperscript{5-12} Such characteristics of these medications have established them as a pillars of cancer therapy.\textsuperscript{13, 14}

This review focuses on the cardiotoxicities of immune checkpoint inhibitor therapy.

**THE IMMUNE CHECKPOINT INHIBITORS**

Immune checkpoint inhibitors, as their name suggests, function by blocking the intrinsic checkpoints that safeguard the body from over-activity of the immune system by down-regulating T cell activity.\textsuperscript{15, 16} The two primary classes of immune checkpoint inhibitors target cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1), both of which directly influence T cells to dampen functionality and prevent autoimmunity.\textsuperscript{16-18} Unfortunately, these checkpoints have been exploited by malignancies to enable immune evasion. In this manner, tumors both escape immunosurveillance and establish immune checkpoints as potent anti-cancer therapeutic targets.\textsuperscript{20, 21}

Yet, despite the generally safe toxicity profile of these medications, clinical trials of immune checkpoint inhibitors have revealed a host of idiosyncratic inflammatory side-effects
that have become known as immune-related adverse events (irAEs). While the precise mechanisms underlying all irAEs remain unknown, biopsies from affected organ systems have demonstrated lymphocytic infiltration, mirroring an autoimmune process. By being systemic therapies, immune checkpoint inhibitors carry the possibility of producing such AEs in any organ system, most commonly targeting the gastrointestinal tract, skin, endocrine glands, and liver. Damage to the pulmonary, musculoskeletal, or cardiovascular systems occur less frequently. However, the current understanding of the spectrum of rare irAEs may be incomplete, as many landmark trials of immune checkpoint inhibitors utilized established threshold rates for AEs. Additionally, an autopsy study of a patient treated with immune checkpoint inhibition revealed widespread inflammatory pathology beyond clinically symptomatic irAEs.

While immune checkpoint inhibition often produces less severe side effects than those associated with traditional chemotherapy, irAEs can be severe and potentially fatal, particularly if involving the cardiovascular system. The currently understood spectrum of cardiac pathology attributed to immune checkpoint inhibitors includes myocarditis, dilated cardiomyopathy, pericardial effusion, and arrhythmias, with autoimmune myocarditis being the best characterized to date. However, this may represent a skewed picture of cardiovascular irAEs, as the studies assessing safety profiles of such agents often do not include routine cardiovascular monitoring, raising the specter of an incomplete sample where only the most severe cases are documented. Regardless, cardiac irAEs pose an important clinical issue, as cases of fulminant myocarditis and rapidly fatal arrhythmias have been documented, illustrating the importance of prompt identification and initiation of treatment for these adverse events.
At this time, there have not been concrete delineations of cardiac function-specific, treatment-specific, or cancer-specific predictors of susceptibility to cardiovascular irAEs.\textsuperscript{38} This places a great importance on understanding the diverse clinical manifestations in which such pathologies may present, and the effective therapeutic options available. Detailed herein is a current documentation and analysis of reported cardiovascular irAEs, in an effort to increase awareness of such potentially severe and underreported events. Following the robust response that has been demonstrated in clinical trials, it is likely that the use of immune checkpoint inhibitors will continue to increase, placing an imperative on prescribing and treating clinicians to understand the possible side-effects.\textsuperscript{14,36,39} While other immune checkpoint inhibitors targeting programmed death ligand 1 (PD-L1) exist, such as atezolizumab, durvalumab, and avelumab, reported cases of cardiovascular toxicity attributed to these medications are limited, and they are not discussed further here.

**Ipilimumab - CTLA-4 Blockade.**

Ipilimumab, an anti-CTLA-4 IgG1 molecule, was first introduced in 2010 for the treatment of melanoma.\textsuperscript{19} CTLA-4 normally functions as an attenuator of the immune system, being up-regulated by activated T cells where it serves as a competitive inhibitor for CD80 and/or CD86 on the antigen presenting cells (APC).\textsuperscript{19,40} By interacting with CD80/CD86, the necessary interaction between CD28 on the T cell and CD80/CD86 cannot be achieved, preventing the requisite co-stimulation for T cell activation, in addition to increasing the functionality of regulatory T cells (Treg).\textsuperscript{19,41} By targeting CTLA-4, the mechanism of ipilimumab prevents the interaction of CD28 on the T cell with CD80/CD86 on the APC, thereby unleashing the immune system from negative regulatory effects and increasing anti-tumor, as well as potentially autoimmune, activity (Figure 1).\textsuperscript{16,18,19}
In preclinical animal studies, the potential for developing severe irAEs with blockade of CTLA-4 is well documented. Mice lacking the CTLA-4 gene have been shown to expire promptly following widespread lymphoproliferation and tissue destruction, corroborating the notion of autoimmunity underlying anti-CTLA-4 irAEs in humans.\textsuperscript{42, 43} Additionally, CTLA-4-knockout mice have been found to develop rapidly fatal myocarditis, a harbinger for the severe cardiovascular irAEs that may develop in patients treated with ipilimumab or other drugs targeting the CTLA-4 checkpoint.\textsuperscript{19, 22, 44} However, such profound autoimmune adverse events are not a certainty with ipilimumab, with only 30% of patients expected to experience an irAE of any type.\textsuperscript{45} Furthermore, those irAEs which do result are often responsive to early initiation of immunosuppression via administration of high-dose corticosteroids.\textsuperscript{27, 36, 46-49}

Currently, there are a wide array of cardiovascular irAEs attributed to ipilimumab treatment, ranging from pericardial effusion and pericarditis, to myocarditis with arrhythmias, to dilated cardiomyopathies mirroring Takotsubo cardiomyopathy.\textsuperscript{23, 49, 50} The documented cases of cardiovascular irAEs illustrate the variety of clinical presentations possible for such phenomena, ranging from generalized malaise and fatigue to multiorgan failure (\textbf{Table 1}).\textsuperscript{23, 49-53} Among the small sample of reported cases, clinical presentations consistent with heart failure exacerbations were the most common, with 70% of patients reporting dyspnea, and 60% experiencing edema and decreased ejection fraction on echocardiography. Less commonly, patients presented with elevated cardiac enzymes (20%) or new-onset atrial-fibrillation (10%).

Of this series of cases, no obvious temporal relationship exists between weeks after therapy initiation and presentation of irAE. The range of therapy duration prior to cardiovascular irAE was 5-36 weeks, with an average of approximately 16 weeks, and median of 12 weeks. This wide range and discrepancy between mean and median of time after exposure that irAEs
occur illustrates a potential difficulty to identifying and treating such phenomena. While the half-life of ipilimumab clearance is approximately 2 weeks, the immune cell proliferation believed to underlie both efficacy and toxicity for this medication proceeds at a much slower pace.\textsuperscript{54} This dichotomy demonstrates that irAEs can occur at virtually any time during treatment with ipilimumab, or potentially weeks and months after therapy has concluded, as the immune system continues to proliferate.

Histologic examination, when available, uniformly demonstrated the presence of inflammation and post-inflammatory changes, such as myocardial fibrosis. This supports the suggested mechanism of autoimmunity, with immunosuppression using high-dose corticosteroids leading to clinical improvement and decrease in serum biomarkers of cardiac damage.\textsuperscript{36, 55, 56} Additionally, T cell receptor (TCR) analysis of a patient with giant cell myocarditis attributed to ipilimumab revealed low T cell clonality within a biopsy of the heart, suggesting that this inflammation may be nonspecific in origin, and the result of chemotaxis rather than a response to cardiac-specific epitopes.\textsuperscript{23}

Additionally, among the documented cases, 6 patients had pre-existing cardiovascular comorbidities, with 33% of these patients experiencing resolution of their irAE after therapy, compared to 100% of patients with no documented cardiovascular comorbidity who experienced irAE resolution. Finally, of the 3 patients who died shortly after identification of their cardiovascular irAE, 2 died due to fatal arrhythmias, while 1 began comfort care measures after developing pneumonia in light of a dismal prognosis.\textsuperscript{51}

In treating cardiovascular irAEs, three therapeutic options have been utilized: immunosuppression with corticosteroids, symptomatic treatment dictated by clinical presentation, or immunosuppression and symptomatic treatment. Of patients treated with some
form of immunosuppression, 66% experienced disease resolution, compared to 100% of patients treated symptomatically alone. However, it is unclear if patients that did not require immunosuppression truly experienced an irAE, as they all also had documented pre-existing cardiovascular comorbidities, and no histologic examination to demonstrate a lymphocytic infiltrate or other evidence of inflammation to support the diagnosis of an irAE. In assessing only those patients who received immunosuppression, the addition of symptomatic therapy did not appear to have an obvious impact on whether resolution was achieved, with 50% of each cohort experiencing resolution.

Previous studies have illustrated a potentially dose-dependent mechanism of ipilimumab related to the frequency of irAE incidence. Specifically, patients treated with 10 mg/kg are reported as experiencing Grade 3-4 AEs a rate nearly double those treated with 3 mg/kg. However, the paucity of case reports prevent assessment of such a relationship for cardiovascular irAEs.23, 26, 27, 47, 49-53, 56

**Nivolumab and Pembrolizumab - PD-1 Blockade**

Pembrolizumab and nivolumab are anti-PD-1 IgG4 molecules that have become a standard of care in melanoma and non-small-cell lung cancer, among other malignancies.10, 29, 31, 33 PD-1 is a receptor induced in activated T cells that normally interacts with programmed death ligand-1 (PD-L1) or programmed death ligand-2 (PD-L2) on the APC, resulting in inhibitory signaling to the T cell, contributing to T cell exhaustion.19, 57 However, the expression of PD-L1 or PD-L2 is not exclusive to APCs, as these ligands are expressed by cells in other peripheral tissues, such as endothelial cells and cardiomyocytes, in an effort to promote immune tolerance and prevent autoimmunity.2, 3, 18, 57
Many solid tumors have been demonstrated to overexpress PD-L1 and PD-L2, thereby co-opting the immune system’s safeguard against autoimmunity to evade immunosurveillance.\textsuperscript{19, 58, 59} By targeting PD-1, nivolumab and pembrolizumab prevent interaction with both PD-L1 and PD-L2, thereby increasing T cell activity and cytokine production, effectively increasing immune activity and mitigating a mechanism of tumor immune evasion.\textsuperscript{19}

As with ipilimumab, preclinical studies assessing the safety of PD-1 blockade revealed potentially severe toxicities. Mice lacking PD-1 have been shown to develop spontaneous cardiomyopathies and autoimmune myocarditis, as well as other autoimmune features such as arthritis and a lupus-like glomerulonephritis.\textsuperscript{19, 44, 60-62} Among cardiovascular adverse events, mice injected with PD-1 deficient T cells developed leukocytic infiltration of cardiac tissue and myocyte death.\textsuperscript{62} Furthermore, preclinical studies have revealed potential risk factors for cardiovascular irAEs with PD-1 blockade, as PD-1 deficient mice with hypercholesterolemia experienced increased inflammation within atherosclerotic lesions, and re-perfused rat hearts following ischemia demonstrated increased PD-L1 expression on cardiac myocytes.\textsuperscript{17, 63, 64}

Similar to the variety of cardiovascular irAEs observed after treatment with ipilimumab, treatment with anti-PD-1 medications has produced a broad spectrum of cardiovascular pathologies, including myositis and myocarditis, bradyarrhythmias and heart block, and pericardial effusion and tamponade; however, the lattermost may also be attributed to a patient’s previous radiation exposure.\textsuperscript{35, 37, 65, 66} A majority of documented cases presented in a manner consistent with an exacerbation of congestive heart failure, with 60% meeting at least one of the following criteria: dyspnea, edema, increased B type natriuretic peptide level, or decreased ejection fraction (Table 2).\textsuperscript{35, 37, 52, 59, 65-70} Additionally, 46% of patients presented with elevated cardiac enzymes, and 40% presented with palpitations or documented new-onset arrhythmias on
electrocardiogram. Less commonly, patients presented with signs of myositis with myalgias, weakness, and fever as the initial symptoms (27%).

The temporal relationship between time after exposure to agent and identified cardiovascular irAE was seemingly unpredictable, with a range of 2-20 weeks, an average of approximately 9 weeks, and a median of 7 weeks. Such an unpredictable pattern again illustrates that cardiovascular irAEs may occur at any time following exposure to anti-PD-1 medications, mandating clinical vigilance. Furthermore, as some patients in this cohort initially presented with myalgias, weakness, fever, and other nonspecific symptoms, it is important to consider any and all new symptoms as potentially associated with immune checkpoint blockade.67

Among documented cases of cardiovascular irAEs associated with anti-PD-1 therapy, only 33% involved some form of histologic tissue analysis. Within this small sample, there was a predominance of lymphocytic infiltration of cardiac tissue, similar to that seen in irAEs attributed to ipilimumab. However, in one patient treated with anti-PD-1 medications, there appeared to be a high rate of clonality among infiltrating lymphocytes in cardiac tissue as well as tumor biopsies.65 Such a finding suggests the possibility of an alternative underlying mechanism to cardiovascular inflammation mediated by anti-PD-1 compared to anti-CTLA-4. In lieu of a generalized inflammation due to chemotaxis, following treatment with anti-PD-1 medications T cells may be responding disproportionately to tissues that express PD-L1 or PD-L2, such as tumors and cardiomyocytes.18, 63, 65, 71

Of the 15 reported cases, 4 had pre-existing cardiovascular comorbidities. From this limited data set it does not appear that pre-existing cardiovascular disease pre-disposes patients to early or more severe irAEs, as the average time after initial exposure within this group was approximately 9 weeks, and 75% experienced clinical resolution. While preclinical models
suggested a possible risk factor of previous ischemia, this cannot be analyzed in this cohort, as no patients with reported irAEs had a previous history of ischemic events.

Overall, irAEs attributed to CTLA-4 blockade are considered to be more severe than those associated with inhibition of PD-1. The limited data set of cardiovascular irAEs attributed to pembrolizumab or nivolumab corroborates this, with death in 30% of anti-CTLA-4-treated patients, compared to death in 20% of patients treated with PD-1 inhibition. Of the 3 anti-PD-1-treated patients who died shortly after identification of cardiovascular irAEs, 2 deaths were attributed to new onset arrhythmias, and 1 to withdrawal of care due to infection and poor prognosis, mirroring the causes of death in the anti-CTLA-4 cohort.

As with treatment for anti-CTLA-4 induced cardiovascular irAEs, three treatment approaches are present in this data set: immunosuppression alone, symptomatic treatment dictated by clinical presentation alone, or immunosuppression with symptomatic treatment. Unlike treatment for anti-CTLA-4 irAEs, steroid-refractory cases, or those which did not demonstrate clinical improvement after corticosteroid immunosuppression, necessitated using additional immunosuppressive agents, such as IV immunoglobulin (IVIG), infliximab, mycophenolate mofetil, and anti-thymocyte globulin (ATGAM). Immunosuppression was commonly used, with 80% receiving some form, and 83% experiencing clinical recovery after treatment. One patient was treated with symptomatic therapy alone, however this case warrants specific mention due to the absence of cardiac damage, with the new-onset tachycardia later attributed to a hyperthyroid state following thyroiditis. Among fatal cases, 1 patient received neither immunosuppression nor symptomatic treatment due to rapid disease progression, and 2 received only immunosuppression, suggesting a possible role for supportive symptomatic treatment to supplement immunosuppression.
In a similar fashion to ipilimumab, the literature suggests a possible dose-dependent mechanism for irAE incidence among patients taking pembrolizumab, with toxicity occurring less frequently in patients receiving a 2 mg/kg compared to 10 mg/kg. However, it is not possible to determine if such a mechanism also exists when exclusively studying cardiovascular irAEs, as no documented cases of cardiovascular irAEs are available for patients treated at a dose of 10 mg/kg pembrolizumab. Regardless, the possibility of increased toxicity at higher doses is important for treating clinicians to consider when monitoring for irAEs.

**Combination Immune Checkpoint Blockade**

In addition to treatment with an individual immune checkpoint blockade, preclinical models have suggested that combination therapy with anti-PD-1 and anti-CTLA-4 agents can provide a synergistic or additive antitumor activity, based on the exploitation of two unique immune checkpoint mechanisms. Indeed, longer progression-free survival and increased complete response rates have been documented with the use of combination immune checkpoint blockade. However, such profound increases in efficacy are accompanied by a significant increase in documented toxicity associated with such treatment, with 55% of patients expected to experience an irAE of any type. Additionally, a recent retrospective and prospective analysis of myocarditis in patients treated with immune checkpoint inhibition found a higher incidence of myocarditis in patients treated with a combination therapy. Furthermore, the irAEs experienced by these patients are severe, with approximately 40% of patients requiring discontinuation of therapy due to untenable toxicity, and a mortality rate of up to 67% in cases of autoimmune myocarditis.

In reviewing documented cases of cardiovascular irAEs with combination immune checkpoint blockade, an increased risk of cardiac toxicity appears to be present compared to
monotherapy with either agent (Table 3). Among 5 reported cases, 3 resulted in patient deaths, an increased mortality rate compared to monotherapy with either agent. Additionally, a marked difference between combination therapy and monotherapy may be the time after exposure that irAEs occur. While the average time after first exposure was approximately 7 weeks, this number was inflated by one case that occurred at week 25, with all other cases occurring by week 2. This limited data suggest a possible increase in irAE severity and rapidity of onset with combination immune checkpoint inhibition. As such, combination therapy may warrant increased clinical vigilance shortly after initiating therapy to promptly identify cardiovascular irAEs.

Within this data set, clinical presentation remained varied, with patients presenting with nonspecific symptoms of fatigue and myalgia, in addition to symptoms of heart failure exacerbation such as dyspnea and edema. As seen with monotherapy, signs consistent with heart failure were the most common presentations, with 80% meeting at least one of the following criteria: edema, dyspnea, or reduced ejection fraction. Other common clinical characteristics at the time of presentation included elevated cardiac enzymes or new-onset heart block, with 60% of patients exhibiting each. Of note, all patients presenting with new-onset heart block progressed to death, despite immunosuppressive and symptomatic intervention.

Histologic analysis was available for 80% of reported cardiovascular irAEs with combination immune checkpoint inhibition therapy. Across all cases, there was a uniformity of lymphocytic infiltration of cardiac tissue, mirroring the histology available with monotherapy with either agent. Additionally, tissue analysis from a patient with fulminant myocarditis revealed a high clonality of T cells within the myocardium and within the tumor, as well as an increased expression of PD-L1 within the myocardium compared to unaffected smooth muscle.
Taken together, these pieces of information suggest the possibility of PD-L1 expression targeting the overactive immune response after treatment with an anti-PD-1 agent, and presents a possible way to identify tissues at risk for irAE after treatment with an anti-PD-1.

Among the documented cases, all patients were treated with some form of immunosuppression. All received corticosteroids, with two receiving more aggressive immunosuppressive agents: 1 patient additionally required infliximab, and 1 patient additionally required both IVIG and infliximab. Of the 3 varieties of immunosuppression used, all were associated with 1 patient death. Three patients had immunosuppression therapy augmented by the addition of symptomatic therapy dictated by clinical presentation; however, 2 of these patients did not recover and died. The high mortality rate observed for cardiovascular irAEs attributed to combination immune checkpoint inhibition despite similar treatment approaches to irAEs associated with monotherapy, again suggests an increase in severity of these events.

Conclusions

Cancer therapy with immune checkpoint inhibition using agents such as ipilimumab, pembrolizumab, and nivolumab remains an exciting and hopeful step forward for patients. However, the antitumor activity afforded by these treatments also carries the risk of collateral damage to other organ systems, including the cardiovascular system. Due to the potential for rapidly fatal arrhythmias and other severe sequelae, prompt identification of patients experiencing cardiovascular irAEs is essential.\(^\text{36,78}\)

The published cases of cardiovascular irAEs associated with immune checkpoint inhibition reveal a diverse array of clinical presentations; however, most patients presented with either heart failure symptoms, acute-onset palpitations, or elevated cardiac enzymes. Therefore, reasonable surveillance measures to detect cardiovascular irAEs would include routine
electrocardiography, measurement of serum concentrations of cardiac enzymes, and
echocardiography for patients undergoing immune checkpoint blockade therapy, as has been
previously suggested in the literature.\textsuperscript{38, 68} Indeed, troponin levels have been demonstrated to
have a predictive value in identifying patients at risk for major cardiac sequelae, such as
cardiogenic shock or cardiac arrest, following immune checkpoint inhibitor-associated
myocarditis.\textsuperscript{36} It is also important to note the limitations of echocardiography as a screening test
for immune checkpoint inhibitor-associated myocarditis, as up to 51\% of cases in a recent study
were found to have normal ejection fractions at time of presentation using this modality.\textsuperscript{36} As
patients may present with myositis as a harbinger to developing a more serious myocarditis, the
assessment of serum creatine phosphokinase also warrants consideration.\textsuperscript{35}

Such steps can lead to prompt identification and initiation of immunosuppression with
corticosteroids or other agents such as ATGAM, for steroid-refractory cases. Additionally,
consideration of symptomatic therapy dictated by clinical presentation, such as diuresis or beta-
blockade, is warranted as a supportive measure during immunosuppression.\textsuperscript{25, 37, 59, 81}

The determination of cardiovascular irAEs continues to present a diagnostic challenge, as
such adverse events remain viewed as rare side-effects of immune checkpoint inhibitors, in turn
limiting the understanding of disease presentations. Further compounding this is the distinction
which must be made between irAEs and pseudoprogression, a phenomenon wherein patients
experience a transient clinical deterioration with signs of disease progression after treatment with
immune checkpoint blockade.\textsuperscript{3} In cases of pseudoprogression, which may involve
cardiovascular symptoms such as pericardial effusion, it is believed that an increase in
inflammation within the tumor causes the transient clinical deterioration prior to spontaneous
resolution, with clinical improvement coinciding with antitumor activity from continued immune
checkpoint inhibition.\textsuperscript{82} This contrasts sharply with irAEs, which are not currently understood to spontaneously resolve, and require immunosuppression to produce clinical improvement.\textsuperscript{82}

As immune checkpoint inhibition becomes a viable treatment option for an increasing number of patients, understanding the potentially severe side effects accompanying these medications becomes essential.\textsuperscript{14, 35, 82} However, until a more complete understanding of the pathophysiology underlying these events can be understood so as to predict those at risk, clinicians must scrutinize each new symptom after initiation of immune checkpoint blockade and maintain a low threshold for suspecting irAEs.\textsuperscript{67}
References


Figure 1. Mechanism of CTLA-4-induced immunosuppression. (A) Cancer cells synthesize and release neoantigens (dots of different colors) that are captured by APCs. These cells present peptides in the context of MHC I molecules/TCRs on the surface of CD8+ cytotoxic T cells within lymph nodes. APCs can also present peptides bound to MHC II molecules to CD4+ T helper cells. T cell activation on TCR signaling requires costimulatory signals transmitted via CD28, which is activated by binding to CD80, and/or CD86, on the surface of APCs. Activated T cells upregulate CTLA-4, which competes with CD28 for binding to CD80 and/or CD86. The interaction of CTLA-4 with CD80 or CD86 results in inhibitory signaling promoting tumour growth. The immunosuppressive activity of CTLA-4 is mediated by downregulation of Th cells and enhancement of Treg cells. (B) CTLA-4 blockade by ipilimumab results in a broad enhancement of immune responses against neoantigen expressing tumour cells, which results in killing of tumour cells. APC, antigen presenting cell; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; MHC, major histocompatibility complex; TCR, T cell receptor; Th cells, helper CD4+ T cells; Treg, regulatory T cell.19

Figure 2. Mechanism of PD-1/PD-L1 pathway-induced immunosuppression within the tumour microenvironment. (A) Tumour neoantigens (dots of different colors) released by cancer cells are captured by APCs. These cells present peptides in the context of MHC molecules/TCRs on the surface of CD8+ cytotoxic T cells. PD-1 is induced on T cells on activation through the TCR and through several cytokines. Tumour cells and other cells in the tumour microenvironment (eg, endothelial cells, mast cells) can express high levels of PD-L1 and/or PD-L2 that binds to PD-1 on T cells, resulting in inhibitory checkpoint signaling that decreases cytotoxicity and leads to T cell exhaustion. Recent evidence suggests that murine and human cancer cell subpopulations
can express PD-1 and promote tumour growth. (B) PD-1 blocking antibodies (nivolumab, pembrolizumab, pidilizumab and so on) inhibit the interaction of PD-1 with both PD-L1 and PD-L2, resulting in enhanced T cell cytotoxicity, TAM activity, increased cytokine production, and ultimately killing of tumour cells. PD-L1+ tumour cells can also induce T cell apoptosis, energy, functional exhaustion and interleukin-10 production. Anti-PD-L1 antibodies (atezolizumab, durvalumab, avelumab) have similar effects, but only inhibit the interaction between PD-L1 and PD-1. APC, antigen presenting cell; MHC, major histocompatibility complex; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; TAM, tumour-associated macrophage; TCR, T cell receptor.\textsuperscript{19}
Figure 1.
Figure 2.