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GAVIN PUBLISHERS

Journal of Oncology Research and Therapy

Review Article

Patel D, et al. J Oncol Res Ther 5: 1094.

DOI: 10.29011/2574-710X.001094

Management of Immune Checkpoint Inhibitor Toxicities: A Thorough Review for Hospitalists

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Citation: Patel D, Singh N, Mubarik A, Patel U, Muddassir S (2020) Management of Immune Checkpoint Inhibitor Toxicities: A Thorough Review for Hospitalists. J Oncol Res Ther 5: 1094. DOI: 10.29011/2574-710X.001094

Received Date: 01 April, 2020; **Accepted Date:** 19 May, 2020; **Published Date:** 25 May, 2020

Abstract

Background: Immune Checkpoint Inhibitors (ICIs) are a new class of immunotherapy drugs used in numerous advance-staged malignancies. The spectrum of the new class of drugs targets inhibitors such as PD-1, PD-L1, and CTLA-4.They can have a wide spectrum of adverse reactions from being asymptomatic to fatal reactions.

Objectives: To conduct a review of guidelines in pharmacology and medical oncology and to address the importance of treating immune related adverse effects of immune checkpoint inhibitors (irAes).

Discussion: Immune checkpoint inhibitors have been proven to prolong the survival of patients with solid tumors and hematologic malignancies. Despite the better prognostic outcome in many malignancies, there have been reported adverse effects in many organ systems, including gastrointestinal, endocrine, pulmonary systems being the most common. Treatment can vary based on the severity of the adverse effect, from observation to high dose steroids and additional immune modulators and intravenous immunoglobulins.

Conclusion: Inpatient use of immune checkpoint inhibitors is becoming more frequent with their promising effects on metastatic malignancies. It is crucial that hospitalists are aware of the side effects and to detect them immediately to prevent further complications.

Keywords: Oncology; Cancer; Oncologic emergencies; Checkpoint inhibitor; Toxicity; Chemotherapy; Immunotherapies; Immune checkpoint inhibitor; Immunotherapy-related adverse events: Death

Introduction

Development of cancer occurs when there is a failure in the surveillance mechanisms, for example, secretion of immunosuppressive cytokines and a negative regulation of cytotoxic $CD8^+$T cells via various checkpoint inhibition [1]. Immune surveillance is the process in which there is detection and elimination of malignant cells by the immune system [1]. This includes mechanisms of enhancing the activation of T cells. They can cause infiltration of immune cells into normal tissues, which may lead to immune-mediated disorders. Almost every organ system can be affected from the skin, colon, liver, lungs, kidneys, eyes, endocrine tissues, and central nervous system [2]. Immune checkpoint inhibitor adverse events are defined as treatment with immune inhibitors, which were not present prior to the initiation of treatment. Treatment can vary from observation, high-dose systemic steroids, immune modulators, and discontinuation of the immune checkpoint inhibitors.

Approved agents for the programmed death -1 receptor that have been known to be used include nivolumab, pembrolizumab, cemiplimab, and cytotoxic T lymphocyte antigen-4 agents like ipilimumab. Drugs working against PD-L1 include atezolizumab, avelumab, and durvalumab [3] Table 1.

Systems Effected	Adverse events
Hematology	Aplastic anemia, autoimmune hemolytic anemia, ITP
Neurology	Peripheral neuropathy, Guillian-Barre syndrome,Transverse myelitis,Myasthenia gravis, Encephalitis, meningitis, encephalopathy, paraneoplastic syndromes
Cardiology	Myocarditis, autoimmune pericarditis
Nephrology	Nephritis
Ophthalmology	Anterior uveitis, retinopathy, uveal effusions, uveomeningitis syndrome
Pulmonary	Pneumonitis, sarcoidosis
Rheumatology	Inflammatory arthritis, vasculitides, SICCA syndrome, SLE, polymyositis
Endocrine	Hypophysitis, thyroiditis, hypo/hyperthyroidism, primary adrenal insufficiency, type I DM
Dermatology	Rash,vitiligo,SJS/TEN and DRESS
Gastro-intestinal/ Hepatology	Colitis, Hepatitis

Laura Spiers, Nicholas Coupe, Miranda Payne (2019) Toxicities associated with checkpoint inhibitors—an overview, Rheumatology 58.

Table 1: Enlists common ICIs with their indications.

Background

Cancer cells have the innate ability to activate different immune checkpoint pathways that have immunosuppressive functions. Immune checkpoint inhibitors are molecules involved in the regulation of immunologic balance. In a normal physiological state, these checkpoint inhibitors are crucial to prevent the onset of autoimmunity. Many immune checkpoint inhibitors have been identified, that have been known to activate or inhibit an immune response [4,5].

Common receptors are the cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed death receptor-1 and 2, and programmed death -1 ligand receptor. The CTLA-4 and PD-1 protein receptors are on the surface of T cells, and the ligand receptors are located on the surface of the cancer cells. PD-1, programmed death receptor are involved with the activation of peripheral T cells and B cells to lead to expression. Their main function is for maintenance of peripheral tolerance. PD-1 has interaction with two ligands, L1 and L2, on B cells, T cells, and dendritic cells [6,7]. The antibodies against the receptors are "Immune normalizers, in the tumor microenvironment. PD-1 has also been associated with autoimmunity, in cases of lupus and glomerulonephritis, arthritis [8] CTLA‐4 was the first immune checkpoint that was targeted in the treatment of cancer. Studies have shown that CTLA‐4 checkpoint inhibitor has reduced tumor growth in mouse models of melanoma, colon carcinoma,and other solid tumors [9,10] .After T-cell activation, CTLA-4 is upregulated on the plasma membrane where it functions to downregulate T-cell function through a variety of mechanisms, including preventing co-stimulation by outcompeting CD28 for its ligand, B7, and also by inducing T-cell cycle arrest [11].

Neurology

Neurologic toxicities have been reported in fewer than 5% of patients taking ICIs [12]. Five broad categories can be established with neurologic adverse events. They consist of neuromuscular junction dysfunction, non-infectious encephalitis and/or myelitis, cerebral artery vasculitis, peripheral neuropathy, and non-infectious meningitis. Strokes, seizures, extrapyramidal syndromes, dementia, sleep disturbances, psychotic disorders, or demyelinating disorders have not been associated with an increased reporting with ICIs. Side effects have been more commonly reported in men than women, ranging from 53 to 65% men depending on the toxicity. Cases largely have been reported in patients with lung cancer and melanoma. The increased reporting of peripheral neuropathy was in part driven by acute polyneuropathies, specifically Guillain-Barre syndrome. Gravbrot, et al. documents 14 cases of GBS, with Nivolumab, Ipilimumab, and Pembrolizumab. Notably, most cases of cerebral artery vasculitis reported were temporal arteritis. Myasthenia gravis also had the highest fatality rates compared with other neurologic toxicities. Two cases have been reported with the use of ipilimumab, and another case with pembrolizumab.

Initial management includes determining interference with daily function, basic history and physical, complete neurological examination, vitamin B12/folate levels, homocysteine levels, and an autoimmune screening. If there is some interference with ADLs, then imaging is the next step. Imaging modalities include MRI of the spine and the brain can be done for diagnosing central nervous effects of checkpoint inhibitors. MRI of the brain can show diffuse dural enhancement with parenchymal sparing for patients who may have meningitis or encephalitis. MRI of the spine can be ordered in patients who have suspected Guillain -Barre or transverse myelitis. MRI of the spine will show uptake of the contrast by nerve fibers in patients with Guillen -Barre. Further investigation including electromyography studies, which conveys reduction conduction velocity. When there is suspected encephalitis, meningitis, encephalitis lumbar puncture can also be done to check for anti-NMDA receptor antibodies, and analysis of the cerebrospinal fluid, which would show increased protein and mononuclear white cell count, and normal levels of glucose. Determining the severity of the symptoms is crucial for knowing how to treat symptoms. Grade one, includes asymptomatic or mild symptoms. These patients can continue immune checkpoint treatment. If the patient has new onset, moderate symptoms, and limited instrumental ADLS, then it is recommended to hold the immune checkpoint inhibitor, start. 5-1 mg/kg prednisolone, and consulting neurology [13]. If the patient is improved to his baseline, a steroidal taper can be done, for at least one month, and then resume treatment. If there is no improvement, treat the patient as a grade 3-4 level toxicity. If the patient is classified as a grade 3 or 4,which is a new onset, severe symptoms, limited self-care ADL, or life threatening, then permanently discontinue the immune checkpoint inhibitor, and increase prednisolone to 1-2 mg/kg/day. If there is an improvement, taper steroids over a one month period. If there is a decline, start other immunosuppressive treatment options [14].

Pulmonology

Pulmonary toxicity caused by immune checkpoint inhibitors has an incidence of around 3-5 %. [15] Patients tend to have nonspecific signs and symptoms of shortness of breath, chest pain, or cough, fever, progressive decrease in exercise tolerance. Physical examination may reveal a normal physical examination to crackles in the lung bases. A median onset of incidence of adverse events was approximately 2.8 months. There has been a variability in onset of symptoms from hours to the first 100 or 200 days.

One of the most common adverse events of causes related to the use of checkpoint inhibitors is pneumonitis. The incidence of pneumonitis can be as high as 7-13%. Pneumonitis has been reported more commonly in phase one trials in non-small cell squamous cell cancer. The incidence of pneumonitis has been associated with the use of anti-PD 1 therapy. The differential diagnosis that should be considered for pneumonitis is myasthenia gravis, myocarditis, reactivation of tuberculosis, opportunistic infections, radiation pneumonitis. While considering the diagnosis of pneumonitis, imaging modality is chest CT scan. Ground glass opacities can be seen, which is nonspecific. Other radiological findings include bilateral diffuse, reticular, consolidative, or Ground Glass Opacities (GGO), predominantly in a peripheral distribution. Radiographic patterns consistent with Cryptogenic Organizing Pneumonia (COP), nonspecific interstitial pneumonia, acute interstitial pneumonitis, acute respiratory distress syndrome, and pulmonary fibrosis are most frequently described and correlate with severity grades of pneumonitis. Pneumonitis can be categorized into four grades. Grade 1 pneumonitis depicts radiographic changes without associated symptoms. Grade 2 pneumonitis may have mild dyspnea and cough that interfere with normal activities of daily living. Severe and life-threatening symptoms describe grades 3 and 4 pneumonitis, respectively. Treatment strategies are based on pneumonitis severity scores. Drug interruption is recommended for severity scores of 2 or higher. The treatment for Grade 1 pneumonitis is to consider delay of treatment, and monitor the patient for symptoms every 2-3 days, with repeat imaging, done every three weeks [16].

Mild-to-moderate cases of pneumonitis are often managed successfully with steroids [17-19]. The recommended medication is intravenous methylprednisolone 0.5-1.0 mg/kg daily or the oral equivalent [19]. The time frame for resolution of mild-to-moderate pneumonitis can be anywhere from 2 to 8 weeks [20]. When symptoms return to near baseline, steroids should be tapered over one month. If there is an improvement in symptoms, checkpoint inhibition therapy can be resumed. If there are no improvement symptoms after 2 weeks or are worsening, pneumonitis should be treated as grade 3-4. Grade 3-4 pneumonitis will present as a new or worsening hypoxia, or life-threatening respiratory compromise. This will require admission to the hospital or intensive care unit. Bronchoscopy and other appropriate diagnostic studies should be performed to exclude infectious or alternative etiologies prior to starting more aggressive intravenous methylprednisolone that should be initiated at a dose of 2-4 mg/kg/day or parental equivalent. If symptoms improve to baseline, steroids should be tapered over at least 6 weeks. However, if symptoms are not improving or worsening after 48 hours, additional immunosuppression should be considered including infliximab, cyclophosphamide, Intravenous Immunoglobulin (IVIG), and mycophenolate mofetil [21].

Another adverse effect that has been known to be associated with immunotherapy is sarcoid like reaction. Ipilimumab and nivolumab are known to cause intrathoracic lymphadenopathy, with an incidence of 5-7%. nivolumab-treated patients. There is a slighter incidence in the female population. Melanoma is more commonly associated with sarcoid like granuloma formation. Median onset of time for development of this reaction was around 6 months. Imaging most commonly shows bilateral hilar

lymphadenopathy [22]. Systemic steroid therapy resulted in complete resolution of de novo sarcoid- like lymphadenopathy in one study [23].

Cardiology

Cardiac involvement from immune checkpoint therapy is variable and can include myocardial, pericardial, and conduction system adverse events. Clinical presentation varies on the type of cardiac toxicity and the degree of involvement. The spectrum of signs and symptoms are nonspecific such as shortness of breath, chest pain, palpitations, syncope and arrhythmias [24].

The most common adverse effects that have been documented are myocarditis, pericarditis, pericardial effusion, cardiac tamponade. From multiple studies, myocarditis has had an increased fatality rate of 27-46% from the use of immune checkpoint inhibitors [25,26]. ICI-related myocarditis usually develops within 17-34 days after initiation of ICI therapy and can progress into hemodynamic instability and need for intensive care. Diagnosing myocarditis includes cardiac troponins, which has a sensitivity of 94-100% [27]. Other tests include ECG abnormalities showing conduction delay, elevated BNP. The American Society of Clinical Oncology (ASCO) recommends echocardiography and a chest xray [28]. Endomyocardial biopsy can also be done for possible ICI related myocarditis [29]. Treatment initially includes stopping ICI therapy. After stopping the treatment, corticosteroids should be administered. If the patient is hemodynamically unstable, administer 1 gm per day. If a patient cannot withstand, then administer mycophenolate mofetil or tacrolimus [30]. Recent studies have shown antithymocyte globulin has been effective in those who have refractory ICI related myocarditis. Other promising interventions include the CTLA4 agonist, abatacept and the anti-CD52 antibody, alemtuzumab [31]. A recent review recommends the use of ACE inhibitors in patients who have ICI related myocarditis and a left ventricular ejection fraction less than 50%, without contraindications to the use of ACE inhibitors [32]. According to ASCO, if a patient has manifested immune checkpoint inhibitor myocarditis with advanced conduction disease or ventricular arrhythmia, administration is not recommended [33]. Pericardial disease is the second most common adverse event after myocarditis. Pericardial effusion, was reported to be found in 7% of patients. Signs of pericarditis are very nonspecific, from shortness of breath and chest pain. Basic evaluation including an EKG, xray, and troponins should be ordered. If pericardial effusion is diagnosed it is recommended to stop ICI therapy. Initial dose of 500-1000 mg prednisone daily followed by weaning off. Additional medications such as colchicine, nonsteroidal anti-inflammatory drugs can be added as well. If refractory to steroids, other medications that can be used are mycophenolate mofetil, infliximab. If a cardiac complication arises, such as cardiac tamponade, an emergency pericardial window must be done.

Another complication that arises is acute coronary syndrome. Pathogenesis has been hypothesized that ICI therapy causes vasculitis, leading to an acute attack of a myocardial infarction. Once ACS is diagnosed, Acs protocol should be initiated, including coronary angiography and percutaneous coronary intervention. Once patient is successfully treated, ICI rechallenge after more than 30 days can be considered [34].

Gastrointestinal

Gastrointestinal side effects are frequent with ICI therapy, especially with CTLA- 4 inhibitors than PD-1/PDL-1 inhibitors common presenting complaints include diarrhea (most common), abdominal pain, nausea/vomiting, fever, anal pain, bleeding, constipation [35].

The various gastrointestinal complications seen with ICI therapy include colitis, hepatitis. Colitis caused by irAE's can be divided into 4 grades based on the frequency of diarrhea/ileus/fever/blood or mucus in stools (grade 4 being the most severe form). The incidence of enterocolitis with PD-1 inhibitors can be as high as 30% one of the potentially fatal complications is bowel perforation, usually with grade 3-4.

Differential diagnosis includes Clostridium difficile, Cytomegalovirus, and Inflammatory bowel disease. Diagnostic work-up should include metabolic and hematologic panel, thyroid panel, erythrocyte sedimentation rate, C-Reactive protein, HIV, hepatitis panel, C. diff toxin, fecal calprotectin, stool ova and parasites, stool cultures, quantiferon for tuberculosis (prior to therapy with infliximab, a Tumor necrosis factor -alpha inhibitor), CT abdomen, endoscopy with biopsy. Lactoferrin can be checked to determine the need for urgent endoscopy. Calprotectin testing can be used to monitor treatment response.

In patients who have grade one symptoms, that does not warrant any imaging. When a CT of the abdomen is done, findings are not specific for checkpoint inhibitor colitis. Imaging will rule out complications such as bowel perforation, abscess, and toxic megacolon. Abdominal CT findings in patients with checkpoint inhibitor colitis can depict mesenteric vessel engorgement, marked thickening of the bowel wall, mucosal hyper enhancement, and a fluid-filled colon 21.22

Endoscopy shows evidence of colonic inflammation. Biopsy should be performed even when there is a normal appearing bowel mucosa on endoscopy. Enteroscopy can be considered to evaluate small bowel as there have been documented cases of enteritis without colitis [35]. Histologic examination reveals neutrophilic and/or lymphocytic infiltrations, rarely abscess and granulomas. These features can be similar to cryptogenic inflammatory bowel disease [36-38].

The timing of the symptom onset varies with each ICI and

can occur within a few days following first dose or weeks after the last dose, Beck et al, noted GI irAE's in 41/137 patients related to Ipilumab (CTLA-4 inhibitor) [36].

Complications with Limumab, nivolumab have a median of onset after 50 days of therapy. Pembrolizumab has a delayed onset of complications, with a median of onset after 6 months of therapy. Treatment of irAE-related diarrhea is primarily symptomatic with corticosteroids reserved for severe toxicities. ICI therapy should be interrupted for Grade 2 and above. Colitis in some cases was refractory to steroid therapy, leading to bowel perforation [36,37]. Refractory cases warrant infliximab therapy. It is essential to keep infliximab therapy in mind for patients rapidly progressing to grade 3 or 4 [37], as response to therapy is usually rapid (within 1-3 days) and a single dose is usually sufficient [35]. An initial clinical response should be followed by a slow steroid taper over at least 8 weeks as relapses are common. CTLA-4 inhibitors may be permanently discontinued in refractory cases, PD-1/PDL-1 inhibitors may be restarted once patient recovers. Repeat endoscopy may be offered to patients prior to re-initiation of therapy.

Another common ICI's usually cause asymptomatic hepatitis usually detected during routine Liver Function Tests (LFT's). Hepatitis caused by irAE's can be divided into 4 grades (grade 4 is the most severe form). Elevation in Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and occasionally bilirubin can be seen with or without an associated fever. Evaluation of other causes of liver injury should also be considered, including concomitant chemotherapy or other medication use, alcohol, thromboembolic or viral etiology. LFTs should be monitored prior to each infusion or weekly in patients with grade-1 LFT abnormality. Work up for grade 2 and above should include viral hepatitis panel, gamma glutamyl transferase, creatine kinase, iron studies. If autoimmune hepatitis is suspected, antinuclear antibody, anti-smooth muscle antibodies, anti-neutrophil cytoplasmic antibodies should be performed. The average onset of symptoms is 6-14 weeks after initiation of ICIs and is dosage dependent. Combination of Ipilimumab and an anti PD-1/PDL-1 has the highest incidence of hepatitis (30%), compared to monotherapy with either Ipilimumab or anti PD-1/PDL-1 (1-6% and 1-10% respectively). The incidence of hepatitis is dosage dependent. Grade 3-4 hepatitis (AST, ALT > 5x above baseline or Total bilirubin > 3x above baseline) is more frequent with combination ICI therapy. Corticosteroids should only be considered when AST/ALT are 3x above baseline. Patients with mild symptoms, grade 1 diarrhea/ colitis that persist for more than 2 weeks, budesonide is started at 9 mg/day for at least 4 weeks. Budesonide is then tapered by 3-mg increments for a total of 4 to 6 weeks of therapy. Prednisone, with a dose of 1 mg/kg per day can be given to patients with persistent grade 1 diarrhea who do not respond to budesonide or patients with grade 2 diarrhea/colitis for more than 3 days. In patients who respond, prednisone is gradually tapered by 5 to 10 mg/week, with the goal of discontinuing prednisone over 4 to 6 weeks. Inflixumab has a potential for hepatotoxicity and hence cannot be used in ICI-related hepatitis. In severe cases (Grade 3-4) with worsening or rebound symptoms despite steroid therapy, immune suppressants such as mycophenolate can be considered [39]. Anti-Thymocyte Globulin (ATG) has been used successfully to treat a case of ICI-related hepatitis [36].

Conclusion

Targeted immunological therapy is one of the upcoming cancer therapies in the treatment of various malignancies. More research is warranted in the field of immunotherapy with the increased use of immune checkpoint inhibitors. Recognizing the toxicities can be difficult given the wide range of differential diagnosis and the vague symptoms. It is crucial that hospitalists can detect the adverse events to prevent worsening prognosis. Some immune related complications remain unknown, and with more research and use, more awareness will be brought to the field of oncology Table 2.

Drug class	Drug Name	Indications and Status	Most common toxicities	Most common high grade toxicities
PD-1 Inhibitor	Nivolumab [38]	Hodgkin's lymphoma	Rash/pruritus (30-34%)	Hepatitis (2-3%)
		HNSCC	Dermatologic (29.1)	
		Advanced lung cancer	Gastrointestinal (11.2%)	
		Metastatic renal cell carcinoma	Endocrine (7.8%)	
		Advanced melonoma		
		High microsatellite instability tumors		
		Merkel cell carcinoma		
	Pidilzumab [39]	Under trial	NR	NR

	Pembrolizumab [39]	Recurrent or metastatic HNSCC	NR	
		Metastatic NSCLC	Dermatologic (10.7)	
		Advanced melanoma	Gastrointestinal (8.1%)	
		Renal cell carcinoma	Endocrine (6.9%)	
		Merkel cell carcinoma		
	Atezolizumab [40]	Melanoma	Diarrhea (18-20%)	Diarrhea (1-2%)
		HNSCC		
		Renal Cell Carcinoma		
		Classical Hodgkins's lymphoma		
		High microsatellite instability tumors		
		Metastatic NSCLC		
		Urothelial carcinoma		
	Durvalumab [40]	Melanoma	Diarrhea (9-10%)	NR
		HNSCC		
		Renal cell carcinoma		
		Classical Hodgkin's lymphoma		
		High microsatellite instability tumors		
		Merkel cell carcinoma		
	Avelumab	Melanoma	NR	NR
		HNSCC		
		Renal cell carcinoma		
		Classical Hodgkin's lymphoma		
		High microsatellite instability tumors		
	Cemiplimab [41]	Advanced cutaneous squamous cell carcinoma	Diarrhea 27% Fatigue (24%), nausea (17%), constipation (15%), and rash (15%)	cellulitis, pneumonitis, hypercalcemia, pleural effusion, and death
		Metastatic disease		
CTLA-4 Inhibitor	Ipilimumab [42]	Approved melanoma after surgery	Dermatologic (43.5%)	Gastrointestinala (7.6%)
		Late stage melanoma	Gastrointestinal (29.0%)	
			Hepatic (3.8%)	
			Endocrine (7.6%)	
			Diarrhea (30-40%)	
	Tremelimumab [42]	Mesothelioma	Diarrhea (30-40%)	Diarrhea (5-10%)

Table 2: Various Classes of Immune checkpoint Inhibitors, and their Side Effects.

Disclaimer: This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and does not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

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