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Chapter

The Flip of the Coin of Personalized Cancer Immunotherapy: A Focused Review on Rare Immune Checkpoint Related Adverse Effects

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Abstract

Immune checkpoint inhibitors (ICIs) are a type of cancer immunotherapy that has provided a tremendous breakthrough in the field of oncology. Currently approved checkpoint inhibitors target the cytotoxic T-lymphocyte-associated protein 4 (CTLA4), programmed death receptor-1 (PD-1), and programmed death-ligand 1(PD-L1). One of the most known complications of these advances is the emergence of a new spectrum of immune-related adverse events (irAEs). In this chapter, we will focus on selected rare or very rare irAEs, shedding the light on the other side of the coin of personalized cancer immunotherapy. We will also discuss general management approach of irAEs with an in-depth look on each one of these rare irAEs. The chapter will also cover principles of immunotherapy rechallenge post-occurrence of irAEs, and the impact of irAEs incidence on the efficacy of ICI. We will discuss some of the rare or very rare irAEs including cutaneous irAEs, immune-mediated Hypophysitis, hematological irAEs, ophthalmic irAEs, checkpoint inhibitor pneumonitis (CIP), neurologic irAEs, infectious irAEs, and cardiac irAEs. This chapter tried to highlight the significance of identifying emerging rare and very rare irAEs while considering initial assessments and management approaches identified in various clinical practice guideline and primary literature data.

Keywords: immune checkpoint inhibitors, adverse effects, pharmacovigilance, rare, irAEs, cancer immunotherapy

1. Introduction

Immune evasion or the ability to evade immune recognition is one of the hallmarks of cancer growth. Cancer cells are able to spread uninhibited by avoiding detection [1] and from that prospective immunotherapy medications were developed and

revolutionized the field of oncology. They have been considered the most important development in cancer treatment over the past decade. With recent advancements in immunology and cancer biology, new classes of immunomodulatory therapy have been developed to aid tumor management [2]. Among the most important targeted pathways of this line of therapy is the inhibition of the cytotoxic T-lymphocyte-associated protein (CTLA-4) and programmed death-1 (PD-1) immune checkpoint. Numerous studies have highlighted the significantly improved survival with the use of immunomodulatory therapy in locally advanced and metastatic cancers including melanoma, lung cancer, urothelial cancer, gastric cancer, renal and hepatocellular carcinoma, and other solid tumors. Trials in other malignancies are ongoing, and undoubtedly the number of drugs in this space will grow beyond the drugs currently approved [2].

Current approved immunotherapy agents are nivolumab, pembrolizumab, cemiplimab, and dostarlimab; all which target PD-1. Moreover, atezolizumab, avelumab, and durvalumab, all of which target programmed death lingand-1 (PDL-1). While ipilimumab is the only drug that targets CTLA-4 [3]. One of the most known complication of these advances is the emergence of a new spectrum of immune-related adverse events (irAEs). Such toxicities are known to be distinctly different from classical chemotherapy-induced adverse events [4–7].

2. Mechanism of immune-related adverse events

The mechanism of irAEs remains unclear; however, it is believed to be related to the immune dysregulation caused by immune checkpoint inhibitors (ICI) [8]. Four potential mechanisms leading to the development of irAEs have been postulated. Firstly, increasing T-cell activity against antigens that are present in tumors and healthy tissues. Secondly, increasing levels of pre-existing autoantibodies. Thirdly, increasing level of inflammatory cytokines. Finally, the direct binding of an antibody against CTLA-4 with CTLA-4 expressed on normal tissues that results in enhanced complement-mediated inflammation [7, 9].

irAEs occur in nearly 90% of patients who are receiving CTLA-4 inhibitors, 70% of patients who are receiving anti-PD-1 or anti-PD-L1, and approximately all patients treated with combined therapy [10–19]. Severity of most of the reported irAEs is grade 1–2. For patients treated with CTLA-4 inhibitors, irAEs mostly involve the skin (44%), gastrointestinal tract (35%), endocrine system (6%), and liver (5%). Although severe irAEs remain rare, they can become life-threatening if not anticipated and managed appropriately [10–20].

The frequency of treatment-related adverse events in general was classified by the World Health Organization as follow: common toxicities arise at the rate of >1% (>1 in 100), uncommon toxicities of 1–0.1% (1 in 100 to 1 in 1000), rare toxicities at a rate of 0.1–0.01% (1 in 1000 to 1 in 10,000), and very rare toxicities at a rate of less than 0.01% [21].

In this chapter we will focus on selected rare or very rare irAEs, shedding the light on the other side of the coin of personalized cancer immunotherapy. We will also discuss general management approach of irAEs with an in-depth look on each one of these rare irAEs. The chapter will also cover principles of immunotherapy rechallenge post occurrence of irAEs, and the impact of irAEs incidence on the efficacy of ICI.

3. General treatment approach of immune-related adverse events

In general, treatment is based on the severity of the observed toxicity defined according to Common Terminology Criteria for Adverse Events Version 5.0, (CTCAEs v5) [22]. For most of patients with moderate (grade 2) irAEs, treatment with ICI should be withheld and should not be resumed until toxicity becomes grade 1 or less. In addition, systemic glucocorticoid should be started if symptoms did not resolve within 1 week. For patients with severe (grade 3) or life-threatening (grade 4) irAEs, treatment with ICI should be permanently discontinued and higher doses of systemic glucocorticoid should be given. Glucocorticoids can be tapered gradually over a minimum duration of 1 month when symptoms subside to grade 1 or less. Use of other immunosuppressive agents such as infliximab, vedolizumab, mycophenolate mofetil can be considered in case of refractory toxicity to glucocorticoids [5, 20].

4. Principles of immunotherapy rechallenge post occurrence of immune-related adverse events

Caution should be considered upon resumption of immunotherapy especially after a severe irAE. After rechallenging with ICI, close follow-up should be performed to monitor for symptoms recurrence [23]. Permanent discontinuation of the ICI is warranted if the ICI is re-challenged and toxicity recur [5, 24, 25]. Prior to re-challenge, patient's tumor status should be assessed. Due to risk of toxicity recurrence following the resumption of the ICI, re-challenge can be considered if the response was partially or fully achieved [26]. A consultation with the irAEs designated specialists might be appropriate before immunotherapy re-challenge.

5. Association of immunotherapy toxicities with efficacy in patients treated with immune checkpoint inhibitors

After a comparison between patients with and without irAEs, it has been noticed that irAEs are associated with either improved efficacy of immunotherapy in terms of favorable response rates and prolonged survival or similar efficacy [27–29]. The interpretation of this finding is that the immune system is sufficiently activated to target patient's cancer and further cause irAEs [30].

In a retrospective analysis that assessed nivolumab efficacy in melanoma patients, treatment-related adverse events of any grade were associated with higher tumor objective response rate (ORR), but no progression-free survival benefit [31]. In patients receiving anti PD-1 or anti PD-L-1 medications an analysis was done on seven trials including 1747 patients on the association between adverse events and outcome, an increase in overall survival was seen in patients with reported adverse events compared to those with no related immune mediated adverse events [27]. It was also concluded in this trial that the relationship between outcome and reported adverse events did not seem to be due to the increased duration of exposure in responding patients [27]. Nevertheless, in a retrospective multicenter study, cumulative time-adjusted risk of disease progression and cumulative time-adjusted risk of death according to both the early-irAEs (≤12 months) and late-irAEs (>12 months) occurrence revealed no statistically significant differences [29].

While in case of high grade rare irAEs; grade 3 or more rare irAEs were associated with inferior overall survival and no impact on PFS [32].

From our point of view, more studies should be done to have a solid conclusion regarding the correlation between immunotherapy toxicities and their favorable impact on patients.

In this chapter we will discuss some of the rare or very rare irAEs including cutaneous irAEs, immune mediated Hypophysitis, hematological irAEs, ophthalmic irAEs, checkpoint inhibitor pneumonitis (CIP), neurologic irAEs, infectious irAEs and cardiac irAEs.

6. Cutaneous immune-related adverse events

Cutaneous irAEs might affect more than half of patients receiving ICI [12]. They are considered the most common toxicity in patients receiving immunotherapy, and out of all irAEs, cutaneous toxicities usually manifest first [33, 34]. The most widely reported dermatological toxicities are inflammatory skin reaction, rash, pruritus, and vitiligo. Rates of cutaneous irAEs were mostly similar in patients receiving anti-PD-1 antibodies and those receiving anti- CTLA-4 antibodies [33]. Severe irAEs were reported more frequently with combination therapy of anti-PD-1 plus anti-CTLA-4 than with monotherapy with either class of agents [35].

The spectrum of irAEs can be categorized into auto-inflammatory and auto-immune responses. Auto-inflammatory side effects are usually nonspecific upregulations of the innate immune system. However, most of the cutaneous irAEs are autoimmune responses. Thus, they represent a more specific activation of adaptive immunity [33]. Cutaneous, autoimmune diseases occur more frequently with anti-PD-1/programmed cell death ligand 1 (PD-L1) than with anti-CTLA-4 therapy [32].

A pooled analysis of mucocutaneous irAEs revealed rare toxicities including urticaria, photosensitivity reactions, xerosis, stomatitis, changes in hair color, alopecia areata and hyperhidrosis [33]. Other reported cutaneous presentations included: ICI-induced dermatomyositis, drug response with eosinophilia and granulomatous, lichenoid, panniculitis-like and lupus-like reactions [36, 37]. For patients with psoriasis, episodes of exacerbation have been reported in patients receiving pembrolizumab, nivolumab or durvalumab [38]. In a single centre experience rare dermatological irAEs were reported as single cases of pemphigoid and bullous dermatitis respectively [32]. Other reported cutaneous irAEs that occurred rarely were vasculitis, neutrophilic dermatosis, erythema nodosum [39–41]. Keratoacanthoma specifically pembrolizumab induced keratoacanthoma type squamous cell carcinoma was reported with a description of eruptive or reactive morphologies [42]. Severe cutaneous irAEs are considered rare. They include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) [43–46].

7. Treatment of cutaneous immune-related adverse events

The treatment of cutaneous irAEs follows the standard treatment of irAEs.

Treatment of mild to moderate pruritis or maculopapular rash is topical emollient, oral antihistamine for pruritus, and topical steroids to affected areas. For moderate cutaneous toxicities, if unresponsive to topical steroids within 1 week, prednisone

0.5 mg/kg/day should be considered [38]. Treatment of severe cutaneous irAEs include the administration of topical and systemic steroids and dermatology consultation. For patients with severe pruritis, gabapentinoids and phototherapy can be considered, intravenous immunoglobulin (IVIG) can be given to severe cases of bullous dermatitis, TEN and SJS [5]. Conservative treatment with cryotherapy, intralesional steroids, electrodessication, curettage, and excision were done for patients having keratoacanthoma [42].

Grade 1 and 2 cutaneous irAEs do not require holding the ICI. However, Immunotherapy should be held in case of severe cutaneous toxicities. In case of severe or life-threatening bullous disease, SJS or TEN. ICI should be permanently discontinued [5]. ICI can be re-challenged if the patient's symptoms have resolved to ≤ grade 1. However, permanent discontinuation of immunotherapy should be warranted in the setting of severe or life-threatening bullous disease (grade 3–4), including all cases of SJS and TEN [5].

8. Immune mediated hypophysitis

It is not uncommon for patients receiving immunotherapy to suffer from endocrinopathies, the most common is hypothyroidism [4]. Central adrenal insufficiency and autoimmune diabetes mellitus are extremely rare adverse events related to ICI. Central adrenal insufficiency can be life threatening when it is severe as it is associated with severe electrolyte disturbance, dehydration, and hypoglycemia [7, 32, 34, 47, 48]. Another well-known endocrine irAE is hypophysitis. Hypophysitis is the inflammation of the pituitary gland (the anterior lobe of the hypophysis) [49].

Hypophysitis was known to be a rare condition, however, with ICI therapy it has become more common [50]. The incidence of hypophysitis was found to be more in patients receiving anti-CLTA-4 therapy as compared to patients receiving anti-PD-1 therapy [51]. It has been reported that hypophysitis occurs in up to 10% of patients receiving anti-CTLA-4 therapy [50, 51]. This might be because pituitary cells can express CTLA-4, thus, anti-CTLA-4 therapy can cause direct damage to the pituitary gland [52, 53]. Furthermore, the incidence of hypophysitis increases with combination ICI therapy compared to ICI monotherapy [50, 51]. Beside the type of ICI therapy, male gender is another risk factor for hypophysitis mainly with anti-CTLA-4 [54]. The onset of hypophysitis is typically 2–3 months after initiation of ICI therapy, however, it may occur even later, and it has been reported 19 months after initiation of therapy [55].

Hypophysitis is generally manifested with vague symptoms. These symptoms include mild fatigue, arthralgias, and behavioral changes. Severe headache and visual changes may also occur. Because the symptoms are non-specific, hypophysitis might be under-diagnosed [5, 20].

Since enlargement of the pituitary gland is rare, the diagnosis of hypophysitis is recommended to be based on clinical presentation and hormonal evaluation rather than imaging [56]. The main consequence of ICI Hypophysitis is deficiency in one or more pituitary hormones. The most reported deficiencies are central adrenal insufficiency, central hypothyroidism, and hypogonadotropic hypogonadism. Around 80% of patients with ICI-induced hypophysitis present with one or more of these deficiencies [52, 53, 55].

Hypophysitis grading depends on the severity of symptoms and can be divided into asymptomatic or mild, moderate but hemodynamically stable, and severe mass

effect or severe hypoadrenalism. Hypophysitis is managed according to the symptoms and hormonal deficiency identified upon presentation. Asymptomatic and mild vague symptoms with no headache does not indicate an interruption of ICI therapy. In such patients, ICI therapy is continued with appropriate hormonal replacement therapy (HRT). On the other hand, patients with mild symptoms (no visual disturbance and no electrolyte imbalance) but hemodynamically stable are recommended to withhold ICI therapy. In addition, oral prednisolone might be initiated. Finally, for severe mass effect symptoms or severe hypoadrenalism, holding ICI therapy and starting IV prednisolone are recommended. In most cases, ICI therapy can be continued. However, most of the patients will require long-term HRT [5, 20, 57].

9. Hematological immune-related adverse events

Hematological irAEs are considered rare in patients receiving ICIs, however, a variety of hematological related toxicities have been reported [58]. These include antibody-mediated hemolytic anemia, thrombotic thrombocytopenic purpura, acquired hemophilia A, autoimmune neutropenia, pancytopenia and autoimmune thrombocytopenia [59–64]. Interestingly, cross-reactions that provoke autoimmune thrombocytopenia after sequential treatment with nivolumab and ipilimumab have been described, this might indicate that the same or similar irAEs might re-emerge on subsequent treatment with a different class of agents [64].

A worth mentioning extremely rare adverse effect is hemophagocytic lymphohistiocytosis (HLH) as it is life threating with a high mortality rate and considered to be a serious complication [65]. Therefore, a patient presenting with severe inflammatory syndrome with associated fever, cytopenias and splenomegaly should prompt a full clinical work- up, including analysis of bone marrow aspirates and/or biopsy samples for the presence of hemophagocytic signs [65].

10. Ophthalmic immune-related adverse events

Ophthalmic toxicity induced by ICI occur in less than 1% of patients treated with ICI therapy [66]. Ocular irAEs can be divided into ocular inflammation, orbital inflammation, and retinal and choroidal disease [67]. The most common ocular irAEs are dry eyes and uveitis. Dry eye syndrome could be severe enough to cause corneal perforation. Uveitis is a type of ocular inflammation and might be anterior, posterior, or panuveitis. Symptoms of uveitis include eye redness, pain, floaters, photophobia, and blurred vision [68]. In patient treated with ICI therapy, dry eye syndrome occurs at a rate of 1–24%. While the incidence of uveitis caused by ICI therapy is reported to range from less than 1% up to 6% [66, 69].

The risk factors of ocular toxicity induced by ICI agents include the type of ICI and the type of cancer [66]. Clinical cases reported that patients on anti-CTLA-4 agents showed higher incidence and severity of ophthalmic toxicity as compared to patients on PD-1/PDL1 inhibitors [67, 70]. Furthermore, ocular toxicity was found to occur more often in melanoma than other solid cancers. This can be explained by the fact of the presence of cross-reactivity between normal choroidal melanocytes and malignant melanoma [70].

Ocular toxicity should be properly recognized and accurately managed because untreated ocular toxicities may lead to vision loss [71, 72]. The treatment of ocular

toxicity depends on the severity of the side effect. Anterior uveitis is treated using topical corticosteroids. While more severe side effects such as ocular inflammation and orbital inflammation are indications for systemic corticosteroids. Artificial tears and other over-the-counter medication can be as symptomatic treatment when it is clinically indicated [5, 68].

11. Immune mediated pneumonitis

One of the worrisome irAEs is the checkpoint inhibitor pneumonitis (CIP). CIP is a term used to refer to pneumonitis induced by ICI. CIP is defined as the occurrence of respiratory signs or symptoms related to new emerging inflammatory lesions viewed on chest computed tomography (CT) after ICI treatment and after exclusion of pulmonary infection, tumor progression, and other reasons [73].

The incidence of CIP was reported to be between 3% and 5% with a fatality rate between 10% and 17%. However, a higher incidence of pneumonitis was noted in patients with non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC) and in patients treated with combination therapy [74, 75]. The median time to the onset of CIP is approximately 2.8 months post-initiation of ICI, and the overall range spans from 9 days to 19.2 months [76].

Some risk factors may predispose patients to develop pneumonitis with ICI therapy. An example of these risk factor is the type of ICI therapy. Patients receiving anti-PD-1 were found to be at increased risk of CIP as compared to patients on anti-CTLA-4 inhibitors. Other risk factors include combination therapy, cancer's primary site, and prior thoracic radiotherapy. In addition, recent literature indicates that a history of asthma and/or smoking may increase the risk of CIP [9, 77].

CIP can manifest as acute, subacute, chronic, and occult. Dyspnea, cough, and decreased activity tolerance are the most common symptoms of CIP. Sometimes, patient may present with chest pain or fever. For patients presenting with fever, the possibility of infectious pneumonia must be excluded. The main signs of CIP include elevation of inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate in most cases. In some patients, velcro crackles can be heard in the lungs on physical examination [73, 74, 76].

The grading of CIP is mainly based on the severity of signs and symptoms. Grade 1 (G1) is referred to asymptomatic or clinically observed CIP only. When common symptoms occur such as shortness of breath and cough, pneumonitis would be graded as grade 2 (G2). While grade (G3) is referred to pneumonitis manifested as severe symptoms that are limiting the activities of daily living. Finally, life-threatening difficulty in breathing would be defined as Grade 4 (G4) pneumonitis [5, 68, 70].

The main therapeutic modality for CIP is corticosteroids as recommended by guidelines on immunotherapy-related toxicity. If no remission is observed after 48 hours, the specific management approach based on the grade should be followed. G1 pneumonitis is managed by delaying the immunotherapy and monitoring symptoms every 2–3 days; in case of worsening, it should be treated as grade 2. While G2 pneumonitis is treated by withholding ICI therapy and initiating an empirical antibiotic in case infection is suspected. If there is no evidence of infection and no improvement occurred within 48 hours, prednisone should be added; if there is no improvement, it should be treated as G3. In G3 and G4 pneumonitis, ICI therapy should be permanently discontinued, and patient should be admitted to the hospital and should be covered with empirical antibiotic. In case there is

worsening or no improvement after 48 hours, IV steroids should be continued, and initiation of infliximab (or mycophenolate mofetil in case of hepatic toxicity) is recommended [5, 68, 76, 78, 79].

The decision to reintroduce the same ICI therapy in a patient who has recovered from CIP must be made based on the individual agent, the severity of the reaction, and the availability of alternative therapies. Patients with G2 pneumonitis can be re-challenged with the same ICI therapy once symptoms are resolved. However, these patients must be monitored closely and more frequently. Mainly all patients with history of CIP require careful and close monitoring because recurrent CIP has been observed in some patients even if they have not been re-challenged with ICI therapy [23, 26, 57].

12. Neurologic immune-related adverse events

Some irAEs such as neurological toxicities recognition and diagnosis is very challenging [80]. There are limited reported data describing neurological manifestations associated with ICI use, with extrapolated incidence of 1–5% highlighting difficult neurotoxicity recognition and possible underreporting [81, 82].

Commonly reported immune relates neurological or neuromuscular toxicities included myasthenia gravis, peripheral neuropathy, multiple sclerosis, Guillain-Barre syndrome, immune-medicated myopathies and encephalitis/meningitis [62, 63, 81–83]. Early recognition and prompt management of immune related neurotoxicity might prevent severe and/or permanent consequences or uncommonly reported fatalities [84].

A common mechanism of irAEs include T-cell activation by the deactivation of inhibitory regulators. However, there is no clear explanation why some patients develop more immune-related neurotoxicity than others [8, 52].

Median time to onset of serious neurological irAEs, of any grade, was 45 days form ICI initiation in melanoma patients with median time to toxicity resolution of 32 days [82].

12.1 Encephalitis

Among neurological manifestations associated with ICI use, encephalitis is considered a rare adverse event with a challenging diagnosis [82, 84]. Although, there is no clear causes of immune mediate encephalitis, around 40–70% of cases were linked to infectious etiologies [85]. On that basis, individualized diagnostic approach to immune associated encephalitis is recommended considering identified clinical presentation. Altered mental status, fever, headache, weakness, neck stiffness, sleepiness, hallucinations or seizure among other neurological sequalae of immune mediate encephalitis were reported by affected patients [82].

With no specified encephalitis grading, initial assessment for suspected immune mediated encephalitis includes neurologist consultation, brain magnetic resonance imaging (MRI), lumbar puncture, electroencephalogram (EEG) to evaluate for subclinical seizures, in addition to complete blood count (CBC), comprehensive metabolic panel (CMP) and autoimmune encephalopathy and paraneoplastic panel [5, 68].

Pertaining to encephalitis associated fatalities, permanent discontinuation of suspected ICI is generally recommended [84]. In-patient admission is warranted for grade 3–4 encephalitis. Corticosteroid trial in the form of methylprednisolone

could be administered and then tapered over 4 weeks upon resolving of symptoms. Enhanced symptoms severity or progression over 24 hours, requires higher doses of methylprednisolone for 3–5 days with IVIG or plasmapheresis. Rituximab may be considered if minimal or no symptoms improvement was obtained after 7–14 days or in cases of positive autoimmune encephalopathy antibody [5, 68]. Additional therapy such as empirical antibiotics and antivirals could be utilized as well. Empiric antiepileptics are reasonable to address any seizure concerns [81, 84].

12.2 Aseptic meningitis

Immune related meningitis is poorly differentiated from encephalitis, mainly in metastatic cancer patients treated with ICI with newly presented seizures or impaired cognitive functions [86, 87].

Unlike, immune medicated encephalitis that is more associated with anti-PD-1 treatment, meningitis is linked particularly with ipilimumab (CTLA-4 inhibitor) use [86, 87]. National Comprehensive Cancer Network (NCCN) 2022 guideline recommended initial assessment involves brain MRI, with or without contrast, lumbar puncture when feasible while considering neurologist consultation [5]. Management of ICI induced meningitis do not significantly differ from encephalitis. Withholding ICI is recommended in mild to moderate toxicity conditions, while permanent discontinuation is required in severe case as per NCCN guideline. Corticosteroids may be considered after ruling out suspected bacterial or viral infections [5].

Rechallenging of ICI after suffering immune medicated meningitis was suggested in cases of mild to moderate toxicity grades while assuring complete symptoms resolution before re-starting immunotherapy agent [5].

12.3 Myasthenia gravis

Immune-mediated myasthenia gravis is an emerging neurologic irAE [88]. Immune-mediated myasthenia gravis induced by ICI use can occur earlier compared to other neurological irAEs (29 vs. up to 80 days) [87].

Concurrent myositis and/or myocarditis are frequently noticed along with immune associated myasthenia gravis, unlike isolated presentation of other immune related neurotoxicity [86, 87].

NCCN 2022 guideline recommend testing for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine phosphokinase (CPK), aldolase and antistriational antibodies, pulmonary function, electromyography (EMG) and considering neurologist consultation while assessing suspected immune-mediated myasthenia gravis. Brain MRI may be considered based on presented symptoms and mainly to rule out central nervous system involvement in disease state. Acetylcholine receptor antibodies testing is not mandated for diagnosis [5].

Upon assessment of toxicity, immune mediated myasthenia graves grading is divided into moderate (grade 2) or severe (grade 3–4).

Regardless of grading, permanent discontinuation of ICI should be carried with immune mediated myasthenia gravis. In-patient care to manage patient symptoms is needed while considering intensive care unit in severe cases. In moderate grade of myasthenia gravis induced by ICI, pyridostigmine and low dose corticosteroids could be initiated. In severe cases or grades 3–4, higher doses of steroids, and initiation of IVIG or plasmapheresis are recommended. Rituximab may be adder in cases of refractory symptoms to IVIG or plasmapheresis [5, 68].

Rechallenging of ICI remains controversial after immune medicated myasthenia gravis, however data of safe re-initiation after complete resolution of symptoms is suggested [89].

13. Infectious immune-related adverse events

13.1 Mycobacterium tuberculosis activation/reactivation

Extended immune response modulation as a response to ICI therapy in addition to administered corticosteroids and/or other immunosuppressants for irAEs management may increase the risk of opportunistic infections [90]. Moreover, such immune response extended manipulation may augment preexisting chronic infections or mask clinical presentations of serious infections such as cytomegalovirus-enterocolitis, pneumocystis pneumonia, infection by varicella-zoster virus, activation of latent tuberculosis, and pulmonary aspergillosis [90]. In addition to that, atypical mycobacterial infection was reported in association with anti PD-1/anti-PD-L-1 therapy [91].

In a review of metastatic melanoma patients treated with different ICIs either anti-CTLA-4, PD-1, and/or PD-L1; the incidence of immune-medicated serious infections was estimated to be 7.3%, with an average time of onset of 135 days from the start of ICI therapy [92]. Highlighted risk factors for developing serious infections included corticosteroids and infliximab use as well as the combination of CTLA-4 inhibitor and anti-PD-1 (mainly nivolumab) [92]. On the contrary, the authors of a retrospective review of melanoma patients treated with ICI concluded that the use of pembrolizumab, an anti-PD-1, was associated with protection against serious infections [92].

Mycobacterium tuberculosis (Mtb) reactivation is an emerging infectious complication of ICI therapy that has been reported with the use of nivolumab [93], pembrolizumab [94] and atezolizumab [95].

Although there is no clear mechanism of action for Mtb reactivation associated with ICI use, preclinical studies on mice [96] and human who administered anti-PD-1 suggested an increase in CD4 T cells production of interferon alfa (INF-α) leading to further bacterial replication [97, 98]. Moreover, extended immunity response could lead to augmented cytotoxicity or extracellular destruction potentiating the growth of Mtb and facilitate disease transmission [99, 100].

A recent systematic review supported the relation between the use of anti-PD-L-1 and Mtb reactivation. Mtb reactivation was disseminated to multiple organs other than the lungs, with reported fatalities [101]. Testing cancer patients for latent Mtb prior the initiation of ICI and use of Mtb chemoprophylaxis, if tested positive, lack the evidence [95], however, is highly recommended for consideration in high-risk individuals [94].

NCCN 2022 guideline recommends baseline testing for latent/active Mtb in patients treated with anti-tumor necrosis factor alfa (TNF-α) that is indicated for the management of irAEs. Moreover, Mtb testing shall not delay the start of anti- TNF-α [5]. There is lack of evidence for the management of immune mediated Mtb reactivation, however, withholding ICI during active infection to avoid possibly excessive inflammatory response is warranted. After anti-Mtb treatment initiation, the safe timing of ICI resumption is not clearly defined. A two-week duration of anti-Mtb prior re-initiation of immunotherapy was suggested [95].

13.2 Hepatitis B reactivation

In relation to PD-1 pathway and hepatitis B virus (HBV), it is previously proven that upregulation of PD-1 is associated with HBV specific T cell dysfunction. In hepatocellular carcinoma patients, PD-L expression was shown to be connected to HBV load [102, 103]. Moreover, it was noted that lung cancer patients with chronic HBV infection have a significantly higher PD-L-1 expression compared to patients lacking HBV infection [104].

Patients with active infections including viral hepatitis B/C or human immunodeficiency virus (HIV) were usually excluded from ICI clinical trials [105]. Considering the possible risk of HBV reactivation for patients with chronic or resolved HBV infections, baseline hepatitis serology should be performed for all patients being treated with ICI with aspartate transaminase (AST)/alanine transaminase (ALT) and HBV deoxyribonucleic acid (DNA) being monitored closely throughout immunotherapy treatment [105–109]. While anti-PD1 was safely administered to lung cancer patient with HBV infection [110, 111], some fatal HBV reactivation associated with durvalumab was reported [105].

14. Cardiac immune-related adverse events

ICI cardiotoxicity most reported manifestations included acute coronary syndrome, arrhythmias, cardiomyopathy, and vasculitis, while myocarditis being mostly reported with high morbidity and mortality rates [112–115]. The exact mechanism of ICI cardiotoxicity is not completely understood. In animal models, ICI use shown to make cardiac cells more vulnerable to injury; this was explained that PD 1, and CTLA-4 pathways appeared to have cardioprotective effects against immune-mediated damage due to stress [116, 117].

The prevalence of reported myocarditis, in an international multicenter registry, was 1.14%, while reaching up to 2.4% with the combination of more than one ICI [118]. The median time of onset is 34 days with majority of presentations occur within 3 months of the start of ICI therapy [119]. Despite that, cardiotoxicity can still present at any time during treatment and even after discontinuation of the therapy [120, 121].

Due to the lack of typical clinical symptoms, and challenges in diagnosis and differentiation from other cardiac disease, the incidence of ICI-related myocarditis is underestimated [112, 113, 122]. Moreover, true incidence of smoldering or subclinical myocarditis is underreported as well [114].

The fatality rate of ICI-related myocarditis increases with the combination of anti-CTLA-4 inhibitors with anti-PD-1/anti-PD-L1, compared to monotherapy with anti-PD-1/anti-PD-L1 [114, 119, 123].

Although risk factors for developing ICPI-related cardiotoxicities are not fully understood, underlying autoimmune diseases is thought to be an independent risk factor [124, 125]. Other risk factors identified in an international registry included use of combination therapy of two or more ICP, CTLA-4 inhibitors, diabetes mellitus, and obesity [119, 126]. Moreover, higher prevalence of ICPI-induced myocarditis was highly reported in patients with pre-existing hypertension (60% vs. 48%, $p < 0.009$), tobacco use (48% vs. 17%, $p < 0.001$), of male gender (65% vs. 55%, $p = 0.02$) and patients on statin (39% vs. 29%, $p = 0.04$) and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (32% vs. 23%, $p = 0.04$) [126].

As per the NCCN 2022 guideline, immediate cardiology assessment along with echocardiogram (ECG) at baseline or with any suspected immune mediated

cardiotoxicity, cardiac biomarkers (troponin I or T, creatine kinase (CK), B-type natriuretic peptide (BNP) or N-terminal (NT)-pro hormone BNP (NT pro BNP) and lipid panel), Cardiac MRI (if possible), and inflammatory markers are needed for assessment and grading of cardiovascular irAEs. Cardiac catheterization and/or myocardial biopsy is considered if myocarditis is suspected [5].

Based on the American Society of Clinical Oncology (ASCO) clinical practice guideline, four categorized grading are defined based on the intensity of clinical presentation into: Grade 1 (G1) and G2 for considerably stable or minimally symptomatic patients, and G3 and G4 for unstable or very symptomatic patients [127].

Further grading criteria such as myocarditis versus pericarditis or pericardial effusion, rather than numerical grading, was applied in NCCN guideline [5].

Withholding the ICI when immune mediated myocarditis is suspected is an essential step in management while initiating further necessary workup [5, 115, 127].

Further management of confirmed ICI- induced myocarditis utilizes high dose intravenous (IV) steroids for 3–5 days. Upon follow up, and if the patient is responding and stable, IV steroids could be switched to oral form and then tapered slowly over 6–12 weeks depending on biomarkers improvement and clinical response. If no such improvement was obtained within 24–48 hours after steroids initiation, additional immunosuppressive therapies could be considered such as: mycophenolate mofetil, tacrolimus, alemtuzumab [128], and abatacept [129]. In hemodynamically unstable patients, further options are suggested including anti-thymocyte globulin (ATG), IVIG, and plasmapheresis [5, 115, 127].

It is still controversial and requires an individualized decision by multidisciplinary team to rechallenge patients who developed ICI-induced myocarditis, where single ICI is recommended upon rechallenging [127]. Severity of cardiotoxicity, status of disease, further treatment options and patient preference should be considered for rechallenging decisions [23, 26].

15. Summary

It has been proven that the use of immunomodulatory therapy has significantly improved survival in locally advanced and metastatic cancers. However, the use of ICIs was associated with some adverse events. This chapter focused on selected rare or very rare irAEs including cutaneous irAEs, immune mediated hypophysitis, hematological irAEs, ophthalmic irAEs, checkpoint inhibitor pneumonitis (CIP), neurologic irAEs, infectious irAEs, and cardiac irAEs. Immune-mediated T cell activation underlines the efficacy as well as possible explanation of most irAEs. In general, treatment of irAEs is decided based on the severity of the observed toxicity which can be defined according to Common Terminology Criteria for Adverse Events Version 5.0, (CTCAEs v5). After resolution of symptoms associated with irAEs, a consultation with the irAEs designated specialists might be appropriate before deciding to rechallenge or permanently discontinue the immunotherapy.

This chapter tried to highlight the significance of identifying emerging rare and very rare irAEs while considering initial assessments and management approaches identified in various clinical practice guideline and primary literature data.

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