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Review

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Neurological Adverse Effects of Immune Checkpoint Inhibitors and Chimeric Antigen Receptor T-Cell Therapy

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Abstract

Immune checkpoint inhibitors (ICPIs) and chimeric antigen receptor (CAR) T-cell constitute recently approved novel therapies targeted to treat a wide number of malignancies. Both the treatments modulate the immune system and can cause a number of immune-related adverse events (irAEs), including polyendocrinopathies, gastrointestinal and neurological complications. This literature review focuses on the neurological side effects of these therapies as these are uncommon and alter the course of the treatment. Neurological complications involve the peripheral and central nervous system, including polyneuropathy, myositis, myasthenia gravis, demyelinating polyradiculopathy, myelitis, and encephalitis. If early recognized, the neurological complications can be treated effectively with steroids to reduce the potential of short-term and long-term complications. Therefore, early identification and treatment of irAEs are needed to optimize the outcomes associated with ICPI and CAR T-cell therapies.

Keywords: Neurological adverse effects; Immunology; Immune checkpoint inhibitors; Chimeric antigen receptor T cells

Introduction

Cancer immunotherapy is at the core of this revolution which targets the immune system of the body and local tumor niche making the tumor more susceptible to immune-mediated killing. The first evidence of targeting the immune system for cancer treatment was the use of bacillus Calmette-Guerin (BCG) vaccine for superficial bladder cancer [1]. Since then, we have gained vast knowledge about the immune system, and the advancement of technology has provided the opportunity to target different aspects of the tumor and immune system interactions for cancer treatment. Immunotherapy mainly acts through increasing the effectiveness of the immune system in recognizing the tumor-specific antigens, by suppressing the checkpoints of immune expressions, by inhibiting the immune-suppressing agents, and by increasing the immune-mediated killing. These mechanisms also act by increasing antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of T-cell immunity through cross-presentation. The main target of immunotherapeutic drugs is to affect the cancer-immunity cycle leading to the generation of self-perpetuating and amplified immune targeting of tumor cells [2].

Immune checkpoint inhibitors (ICPIs) and chimeric antigen receptor (CAR) T-cells therapy are two recent immune targeting treatment strategies with very effective outcomes. Pembrolizumab, ipilimumab, nivolumab are checkpoint inhibitors approved by the Food and Drug Administration (FDA) for melanoma, lung cancer, renal cell cancer and are being investigated for other types of cancer. Checkpoint inhibitors nivolumab and pembrolizumab have been studied in classical Hodgkin lymphoma as well with good efficacy profiles [3]. These therapies have also been found to be having a good efficacy profile in terms of overall survival in patients with renal cell cancer [4]. Similarly, CAR T-cell therapy is approved for B-cell precursor acute lymphoblastic leukemia (ALL), large B-cell lymphoma including diffuse large B-cell lymphoma (DLBCL) arising from follicular lymphoma, multiple myeloma, and mantle cell lymphoma. Although these therapies have led to increased survivability of the patients but also led to incidences of immune-related side effects in around 2-3% of patients.

As ICPIs and CAR-T cell therapy have become an integral part of cancer immunotherapy, it is essential for physicians, oncologists, and neurologists to be aware of its toxic effects succinctly. In this review, we have summarized the etiology, clinical presentation, diagnostic tests, and treatment of

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Table 1. Types of Cancer Immunotherapy, Commonly Used Drugs, Target Sites and Mechanism of Action

Types of immunotherapies	Drugs		Target site and mechanism of action
Checkpoint inhibitor [2]	Pembrolizumab, nivolumab, dostarlimab-gxly	PD-1 receptors	Removes inhibitory signals of T-cell activation
	Atezolizumab, avelumab, durvalumab, cemiplimab	PD-L1 sites	Enables tumor-reactive T cells to mount an effective antitumor response
	Ipilimumab	CTLA-4	
CAR T-cell therapy [3, 4]	Tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene marualeucel, brexucabtagene autoleucel	CD-19-directed	Chimeric/genetically modified T cell expressing receptor for tumor specific antigen
			MHC independent T cell binding with specific antigens
	Idecabtagene vicleucel, ciltacabtagene autoleucel	BCMA-directed	$CD4^+$ and $CD8^+$ T cell-mediated tumor lysis via perforin and granzyme exocytosis, death receptor signaling

CRT: chimeric antigen receptor; PD-1: programmed death 1; PD-L1: programmed death-ligand 1; CTLA-4: cytotoxic T-lymphocyte antigen-4; MHC: major histocompatibility complex; BCMA: B-cell maturation antigen.

various neurological side effects of these immunotherapeutic agents.

ICPIs

Background

The immune system exerts strong selective pressure on tumor cells for survival, and tumor cells adapt by immunoediting and opting for immune tolerance and suppression [5]. Immune checkpoints are the rate-controlling steps that help immune self-tolerance by regulating the amount of immune activation and also help tumor cells in avoiding immune-mediated killing. The first concept of using immune checkpoint blockade against cancer cells was given by Leach et al in 1996, from Allison's lab, where blockade of the inhibitory effect of cytotoxic T-lymphocyte antigen-4 (CTLA-4) by antibody led to T-cell activation that increases the immune reactivity against the cancer cells [6]. This landmark study led to the development of checkpoint inhibitors as a cancer therapy option. The current checkpoint inhibitors mainly target the two specific molecules, i.e., CTLA-4 and programmed death 1 (PD-1), which are involved with immune regulatory mechanisms and maintaining immune responses in the physiological range.

The antigen-presenting cells (APCs) capture and present tumor antigens to naive T lymphocytes in the lymph nodes. In order to activate the naive T cell, the T-cell receptor (TCR) must interact with the major histocompatibility complex (MHC) molecules on the APCs, as well as costimulatory pathways [6]. Costimulatory and inhibitory signals control the T-cell response. Immunological checkpoints are inhibitory signals that control immune responses and prevent autoimmunity. Antibodies targeting against inhibitory molecules expressed by T cells, such as CTLA-4 and PD-1, and PD-1 ligand expressed by tumor cells, are the basis [7] of ICPI therapy (Table 1) [2-4].

Immune-related adverse events (irAEs) are very common with the checkpoint blockade and may be seen in around 25-90% of patients treated with ipilimumab (anti-CTLA-4 antibody), in 70% of patients treated with the PD-1 blockers - nivolumab and pembrolizumab, and around 95% in combination therapy group [8]. Most affected sites are skin, gut, and rarely affected sites are liver, endocrine, and nervous system. Neurological side effects of checkpoint inhibitors vary from simple fatigue to very rare yet complicated adverse reactions of necrotizing encephalitis [9]. Hemophagocytic lymphohistiocytosis (HLH) can also be a treatment complication from these check point inhibitors, but difficulty arises in the etiology as it has an established association with underlying malignancies as well [10].

Although the specific mechanism of ICPI causing neurological irAE is unknown, worsening of pre-existing autoimmunity and potentiation of autoimmune paraneoplastic diseases have been suggested [11]. The increased immune reactivity either acts by increasing the antibodies against the self-antigens, infiltration of clonal T cells similar to that present in tumor or increasing the cytokine level acting against the normal healthy tissue [12].

The incidence of neurological side effects varies according to the therapy used, with 3.8% in anti-CTLA-4, 6.1% in the anti-PD-1 antibodies group, and 12% in patients on combination therapy [13]. The symptoms generally occur within 6 - 12 weeks of starting the ICPI but sometimes may occur immediately after starting the medication or months after discontinuation of ICPI. These side effects were related to the effect of ICPI efficacy and had some relation to anti-PD-1 doses as well [14]. Neurological symptoms are highly heterogenous and vary from grade 1 - 2 adverse effects like headache, fatigue, dysgeusia, dizziness to grade 3 - 4 symptoms, and sometimes even death of the patient. The more complex grade 3 - 4 neurologic adverse events can affect the central nervous system, i.e., hypophysitis, encephalitis, aseptic meningitis, or the peripheral nervous system, i.e., acute demyelinating polyneuropathy, myasthenia gravis (MG), and necrotizing myositis. The Common Terminology Criteria for Adverse Events (CTCAE) rates the severity of irAEs based on clinical severity, ranging from grade 1 with minimal symptoms, grade 2 with moderate symp-

Table 2. Neurological Side Effects of Cancer Immunotherapy

Immunotherapy	Neurological side effect	Probable pathogenesis
Checkpoint inhibitor [7, 8, 10]	Central: encephalitis (0.1-0.2%), aseptic meningitis (0.1-0.2%), hypophysitis (10% in CTLA-4 AB)	Antibodies against the self-antigens
	Peripheral: polyneuropathy (3%), acute demyelinating polyneuropathy (0.1-0.2%), myasthenia gravis (0.1-0.2%), and necrotizing myositis	Infiltration of clonal T cells similar to that present in tumor
		Increase in the cytokine levels acting against the normal healthy tissue
		Worsening preexisting autoimmunity
CAR T-cell [16-18]	ICANS: tremors, headache, lethargy, memory impairment, language difficulties, encephalopathy, agitation, seizures, myoclonus, ataxia, meningismus	Disruption of the blood-brain barrier
	Progressive multifocal leukoencephalopathy	Passage of inflammatory cytokines (IL-6, IFN-γ, TNF-α) and lymphocytes into CSF
	Posterior reversible encephalopathy syndrome (PRES)	Endothelial and pericyte activation, consumptive coagulopathy, widespread inflammation
	Intracranial hemorrhage	Parenchymal basement membrane and vascular disruption, with cerebral edema, hemorrhage, infarction, and necrosis, and neuronal death
	Movement and neurocognitive treatment-emergent adverse events	

CTLA-4: cytotoxic T-lymphocyte antigen-4; AB: antibody; CRT: chimeric antigen receptor; ICANS: immune effector cell-associated neurotoxicity syndrome; IL: interleukin; IFN: interferon; TNF: tumor necrosis factor; CSF: cerebral spinal fluid.

toms, to grade 3/4 with life-threatening symptoms [15]. Hence, this severity grading can be used to guide management (Table 2) [7, 8, 10, 16-18].

Peripheral nervous system

MG

Antibodies targeting neuromuscular junction or muscle-specific tyrosine kinases cause MG, a B cell-mediated autoimmune disease. ICPI therapy was linked to MG in a case series, with antibodies to acetylcholine receptors being found in around 60% of individuals. The majority of these cases had new-onset MG, and there were fewer cases of disease exacerbation. Pembrolizumab-related MG, for example, had 70% *de novo* instances, nivolumab had 57.1%, and ipilimumab had 100% *de novo* cases of all patients [19]. The myasthenic syndrome can present, ranging from ocular symptoms such as ptosis and diplopia to generalized weakness, dyspnea, and dysphagia. Patients should undergo electromyography (EMG) testing for acetylcholine receptor and muscle kinase-specific antibodies. The onset of MG varied between 4.5 and 6 weeks or more on average. The mortality rates can be varied based on the type of immunotherapy used [19]. These patients require early and intensive monitoring due to their severe clinical presentation and rapid decline, which frequently necessitates intensive care unit (ICU) admission. Early treatment with high-dose corticosteroids is recommended, which is especially beneficial when myositis occurs concurrently. Plasma exchange and intravenous immunoglobulin (IVIG) are also used in treatment to escalate therapy [9]. As with other adverse effects, it would be prudent to discontinue the ICPI therapy.

Myositis

ICPI-induced myositis might be part of an overlapping condition that includes MG and acute inflammatory demyelinating polyneuropathy (AIDP) [9]. Myositis was the most common adverse event reported in a large case series of ICPI-induced neuromuscular side effects. It usually presents with muscle pain and gradual weakening, affecting primarily the proximal limbs [16]. Predominant lymphocytic infiltrates were seen in the histopathology review, with some reports indicating predominating $CD4^+$ endomysial lymphocytic infiltrates and others indicating predominating $CD8^+$ cells [20]. A creatine kinase (CK) levels, EMG, and myositis antibody panel constitute the workup [7]. It is associated with high levels of CK. Autoantibodies associated with myositis are often negative; however, anti-PL-7, anti-PL-12, anti-SRP, and anti-Ro antibodies have been reported. As a result, early detection and treatment with immunosuppressants are critical [16].

Peripheral neuropathy

ICPI therapy has been linked to immune-mediated neuropathy such as AIDP and chronic inflammatory demyelinating

polyneuropathy (CIDP) [9]. It has a wide range of clinical manifestations that impair the motor, sensory, or autonomic nervous system. Multiple cranial nerves can be affected, with the facial vestibulocochlear, and optic nerves being the most commonly affected [7]. It is also linked to polyradiculopathies, also known as Guillain-Barre syndrome (GBS)-like syndrome, which causes motor and sensory impairments, affecting the extremities. Nerve conduction studies and EMG are vital to differentiate it from cancer-induced neuropathies. In an article by Thaipisu et al, CIDP was shown to be linked to a high level of cerebrospinal fluid (CSF) protein. In this case, the symptoms began 1 month after CPI therapy and progressed over the next 2 months which did not respond to steroids, IVIG, and infliximab, but were later alleviated with tacrolimus [21].

Central nervous system

Hypophysitis

Hypophysitis can affect up to 10% of the patient receiving anti-CTLA-4 antibodies and maybe because of expression of CTLA-4 on pituitary cells, which causes antibody formation, complement deposition, and mononuclear cell infiltration in the pituitary [17]. Patients using anti-PD1/programmed death-ligand 1 (PD-L1) therapy are far less likely to develop this condition. It typically manifests as headaches, neck pain, visual abnormalities, vertigo, and weakness [11]. However, the pituitary's actions on the adrenal cortex, thyroid, and other organs/glands can cause a wide range of symptoms. If a diagnosis is suspected, hormone levels from the pituitary, thyroid, adrenal, and gonadal glands should be tested. A brain magnetic resonance imaging (MRI) can confirm the diagnosis [22]. Only one hormonal axis may have been affected in some circumstances, while others remain unaffected. Symptoms usually develop 6 weeks after starting therapy; however, symptom remission can take up to 20 weeks and is linked to permanent pituitary dysfunction [23]. Management differs on the basis of grade of toxicity. We may or may not hold off the ICPI therapy in grade I or II toxicity. However, it becomes imperative to hold off on the ICPI therapy in cases of higher grades of toxicity (grade III or IV) until the patient is stabilized on hormone replacement. Corticosteroid therapy should be initiated prior to hormone replacement therapy to treat this condition [18].

Aseptic meningitis

Aseptic meningitis and encephalitis have a very low incidence of 0.1-0.2% in patients receiving ICPI with symptoms varying widely in both conditions. Fever, headaches, and neck stiffness are some of the common symptoms of aseptic meningitis [11]. It may co-occur with encephalitis and infectious studies usually come up negative, with lymphocytosis and high opening pressure seen in a CSF analysis. MRI may show diffuse leptomeningeal enhancement. The treatment is high-dose steroids which have shown a good response [9].

Encephalitis

The median onset of the presentation of encephalitis was around 55.5 days in a large database analysis. Confusion, aphasia, agitation, altered mental status, and psychiatric symptoms are common signs and symptoms [15]. T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities can be seen on MRI; however, normal findings do not rule out the diagnosis. Many cases of encephalitis were related to paraneoplastic antibodies, including N-methyl-D-aspartate receptor antibodies and contactin-associated protein-like 2 or anti-Hu antibodies; and tests for these antibodies must be conducted in patients suspected of autoimmune encephalitis after ICPI. However, the absence of antibodies does not exclude the diagnosis. Early detection and intervention may increase the likelihood of resolution. The research also revealed that stopping ICPI treatment was linked to better patient outcomes [15]. Patients with a suspected infectious etiology are frequently treated empirically with antibiotics and antiviral treatment until the etiology is ruled out. The majority of patients were treated with intravenous (IV) steroids, and half of them required IVIG due to deteriorating symptoms, according to a review of six cases of CPI-induced encephalitis.

Both aseptic meningitis and encephalitis are graded as mild, when symptoms are not interfering with activities of daily living (ADLs); moderate, when ADLs are moderately compromised, or any cranial nerve is involved and severe when it warrants aid because of limited ability for self-care. Regardless of the severity of symptoms, ICPI should be held and resumed only upon shared decision making with the patient, who understands the risks and benefits of the therapy.

Mild-moderate aseptic meningitis should be empirically treated with IV antivirals (acyclovir) and IV antibacterial therapy until CSF results are negative for infection. The patients may be monitored off antimicrobials thereafter. Oral or IV steroids may be considered for moderate-severe symptoms. For the treatment of mild-moderate encephalitis, patients should empirically receive IV acyclovir, until polymerase chain reaction (PCR) for herpes simplex virus (HSV) is negative along with a trial of methylprednisolone 1 - 2 mg/kg. Symptoms progressing to the severe grade treatment with pulse steroids methylprednisolone 1 g daily for 3 - 5 days along with IVIG 2 g/kg over 5 days may be considered.

Other neurologic side effects

Transverse myelitis has also been reported as a side effect of ICPI. This case responded well with treatment with steroids along with discontinuation of ICPI treatment [22]. ICPI therapy has also been linked to multiple sclerosis (MS), which is characterized by demyelinating lesions in the brain and myelin and possible optic nerve involvement [11]. It can lead to MS exacerbation as well as *de novo* cases. Also, ICPI treatment can also lead to *de novo* vasculitis [9]. In a systemic review, 20 pathologically confirmed central and peripheral nervous system vasculitis cases were found out of 53 probable cases, with the majority involving medium or large vessels

Table 3. General Investigations and Management of Immune-Related Adverse Events (irAEs)

Immunotherapy	Investigation	Management
Checkpoint blockade		
Central nervous system [25]	MRI brain	Withholding ICI therapy
	CSF analysis	Steroids
	Check hormone levels in cases of endocrine dysfunction	IVIG
	EEG	Plasmapheresis
	Paraneoplastic antibodies	Hormone replacement therapy as indicated
	Other laboratory tests to rule out alternative diagnosis	Immunosuppressants
Peripheral nervous system [10]	MRI brain/spine	
	Electroneuromyography, muscle biopsy if needed	
	Autoantibody workup	
	Laboratory tests including CK levels	
CAR T-cell therapy [26, 27]	MRI brain or CT head	Use ICANS grading system to grade disease severity and manage accordingly: grade 1, supportive; grade ≥ 2, add corticosteroids; grade ≥ 3, add close monitoring in the ICU
	CSF analysis	
	EEG	
		Supportive management for seizures and raised intracranial pressure
		Can use tocilizumab when concurrent with CRS
		Can consider siltuximab, anakinra, and IVIG for refractory cases

ICI: immune checkpoint inhibitor; CAR: chimeric antigen receptor; ICU: intensive care unit; IVIG: intravenous immunoglobulin; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; CSF: cerebral spinal fluid; EEG: electroencephalography; MRI: magnetic resonance imaging; CT: computed tomography; CK: creatine kinase.

[24] (Table 3) [10, 25-27].

CAR T-Cell Therapy

Background

Immunotherapy, with CAR-expressing T cells has been a major advancement in the management of hematologic malignancies. Autologous or allogeneic T-cells are genetically modified to express a CAR that consists of an extracellular domain that binds to target molecule on tumor cells, a transmembrane domain, and an intracellular domain that signals T-cells activation [28]. This intrinsic activation mechanism makes T-cell activation independent of the need for MHC-epitope presentation [29].

CAR T-cell therapy has shown excellent response rates of 50-80% in refractory B-cell lymphoma [30], and 65-90% in ALL [31]. Currently, there are six FDA-approved CAR T-cell products, tisagenlecleucel used for relapsed/refractory B-cell precursor ALL or large B-cell lymphoma, axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma including DLBCL arising from follicular lymphoma, lisocabtagene marualeucel for relapsed/refractory large B-cell lymphoma, brexucabtagene autoleucel for relapsed/refractory mantle cell lymphoma and recently for relapsed/refractory B-cell precursor ALL, and idecabtagene vicleucel and ciltacabtagene autoleucel for relapsed/refractory multiple myeloma (Table 1) [2-4].

A widely observed toxic effect of CAR T-cell therapy is cytokine release syndrome (CRS), which occurs due to activation of the innate immune system [32]. CRS presents with fever, with or without signs of hemodynamic instability such as hypotension, hypoxemia, tachypnea, and tachycardia [33]. Tocilizumab, anti-interleukin-6 (IL-6) receptor antibody has shown an excellent response in CRS management by mitigating downstream effects of IL-6, which is central to CRS pathophysiology [34].

Apart from CRS, another common adverse effect of CAR T-cell therapy is its neurotoxicity. Initially known as (CAR T-cell related encephalopathy syndrome (CRES), the neurotoxic effects of CAR T-cells are now largely categorized as immune effector cell-associated neurotoxicity syndrome (ICANS). ICANS represents a wider term including neurotoxic effects of other cell therapies and targeted antibodies [35]. In addi-

tion to ICANS, other neurologic complications like progressive movement and neurocognitive treatment-emergent adverse events [36], multifocal leukoencephalopathy, posterior reversible encephalopathy syndrome (PRES), and intracranial hemorrhage can also occur after CAR T-cell therapy [37]. It is essential to optimally investigate and manage ICANS, which is a potentially fatal condition.

ICANS

Risk factors

The incidence of neurotoxicity was found to be 48% in a study of 100 cancer patients being treated with CAR T-cell therapy [25]. Incidence varies depending on the specific CAR T-cell therapy product and underlying disease being treated. For instance, the use of a humanized or murine single-chain variable fragment (scFv), the use of hinge and transmembrane domains derived from either the CD28 or the CD8α molecule, and the use of CD28 costimulatory moieties have been implicated with the occurrence of ICANS [38]. Also, as compared to CAR T-cells targeting CD-19 tumors, a lower incidence of ICANS has been noted for non-CD-19 CAR T-cells targeting hematologic malignancies [26].

In phase I/II clinical trial of ALL patients treated with JCAR014, severe ICANS was associated with several independent factors such as cyclophosphamide and fludarabine lymphodepletion, bone marrow disease burden, and pre-existing neurologic comorbidity. Several clinical indicators, such as high serum IL-6, fever, high monocyte chemoattractant protein-1 (MCP-1) in the first 36-h post-infusion have been associated with grade 4 or higher neurotoxicity with 100% sensitivity and 97% specificity [39]. Other factors such as higher levels of serum C-reactive protein (CRP), various serum cytokines, and CRS symptoms such as fever after beginning CAR T-cell therapy, have also been considered as predictors of ICANS occurrence. In a recent study, patients with clonal hematopoiesis of *DNMT3A, TET2*, and *ASXL1* genes were related to higher incidence of ICANS compared to clonal hematopoiesis negative patients [40].

Pathophysiology

Pathogenesis of ICANS is not completely understood and there has not been any clear association with imaging or CSF abnormalities. Several studies have considered it to be a result of systemic inflammation which leads to endothelial disruption, consumptive coagulopathy, and a breach in the blood-brain barrier (BBB) [34]. In patients with ICANS, CSF cytokine levels were higher than expected and comparable to the serum cytokine levels, supporting the breach in the BBB as a plausible mechanism [41]. High concentration of IL-6, interferon (IFN)-γ, tumor necrosis factor (TNF)-α along with CAR T-cells are also found inside the CSF. Those high levels of inflammatory cytokines induce endothelial cell activation, resulting in release of angiopoietin-2 (Ang-2) and von Willebrand factor (VWF) from endothelial Weibel-Palade bodies, and the released VWF binds activated endothelium and sequesters platelets. [39]. Increased permeability of the BBB due to the endothelium activation allows a higher concentration of serum cytokines to transit into CSF, including IFN-γ and TNF-α, initiating a feed-forward loop of continued endothelial cell and pericyte activation. This feed-forward loop can cause breakdown of the parenchymal basement membrane and vascular disruption, with cerebral edema, hemorrhage, infarction, and necrosis, and neuronal death. Along with the passage of cytokines, this BBB breach can also lead to the passage of lymphocytes into CNS, as suggested by lymphocyte infiltrates seen in some brain autopsies of ICANS patients [42]. In phase I/II clinical trial of ALL patients treated with JCAR014, endothelial activation, parenchymal necrosis, and microhemorrhages were seen in brain autopsies of patients who developed cerebral edema [43]. Also, high serum ferritin levels have been observed in ICANS, supporting the role of macrophage activation [44].

Symptoms

ICANS can present early simultaneously with CRS, after CRS resolution, or rarely without associated CRS. Although classically, ICANS is thought to present as encephalopathy with preserved alertness, clinical manifestations can be vague and variable in severity [41]. Early symptoms can be mild such as tremors, headache, lethargy, and mild impairment of attention, memory [25]. Mild visual symptoms, mimicking migraine, can also be seen. Language difficulties are very specific to ICANS and are often recognized as the most common sign of severe neurotoxicity. In a phase I trial of CAR T-cell therapy, expressive dysphagia was the first symptom of ICANS in 86% of severely affected patients [41].

Severe symptoms can involve encephalopathy, tremors, agitation, and seizures [32]. Encephalopathy can have waxing and waning symptoms, with or without impulsivity and emotional lability. Patients can also have myoclonus, ataxia, and meningismus [27]. The most devastating complication is cerebral toxicity leading to cerebral edema which could be fatal. However, it has not been a significant feature in multiple major CD-19 CAR T-cell studies. Interestingly, some cases can mimic stroke with focal neurologic deficits like weakness [41] (Table 2) [7, 8, 10, 16-18].

Investigations

As the symptoms of ICANS are highly nonspecific and mimic other conditions, the diagnostic tests ordered are aimed at ruling out isolated or coexisting conditions such as infections, drug toxicity/induced, neurologic invasion of the primary malignancy, or disease relapse. A full neurological exam including fundoscopy should be done. Workup includes neuroimaging with MRI brain or a computed tomography (CT) scan of the head. An MRI can show white matter hyperintensities, vasogenic edema, microhemorrhages, however it can often be

normal even with high-grade ICANS [25].

Further testing with CSF analysis should be carried out if there are no contraindications, which can show elevated protein and mild pleocytosis. Electroencephalography (EEG) can be done in patients suspected to have seizures or nonconvulsive status epilepticus [32]. EEG [28] most commonly shows diffuse or focal slowing, frontal intermittent rhythmic delta activity (Table 3) [10, 25-27].

Management

Although there is no definite guideline for the time to begin CAR T-cell toxicity management, earlier administration of tocilizumab has been shown to reduce the incidence of severe CRS in patients on CTL019 therapy [45]. Performing a neurologic assessment prior to starting CAR T-cell therapy and for 10 days post-infusion is highly recommended. After 10 days, the patient can be transitioned to ambulatory care provided they remain within 1 h of a treatment center for the initial 28 days post-treatment.

Since the development of CAR T-cell therapy, several scoring guidelines have been developed to grade CAR T-cell toxicity. In 2018, CAR T-cell therapy-associated-TOXicity (CARTOX) Working Group provided recommendations for assessment of CAR T-cell-associated neurotoxicity, then known as CRES [28]. In 2019, the American Society for Transplant and Cellular Therapy (ASTCT) group coined the term ICANS and published a modified ICANS grading system [46]. Widely used today, the ICANS grading system is based on assigning a score between 1 to 4 based on these five variables: immune effector cell-associated encephalopathy (ICE) score, level of consciousness, seizure activity, motor activity, and elevation of intracranial pressure (ICP). The ICE score, in turn, analyses orientation, attention, writing, naming, and ability to follow commands [46].

Grade 1 ICANS should be managed supportively. For grade 2 or higher, the mainstay of treatment is corticosteroids, either dexamethasone or methylprednisolone. For grade 3 or more, closer monitoring in ICU is recommended for patients with grade 3 or higher ICANS [32]. For patients with a high risk of ICANS, antiepileptics such as levetiracetam can be given for seizure prophylaxis prior to starting CAR T-cell infusion. For patients who develop seizures, levetiracetam has been widely used as a treatment of choice [26]. Raised ICP can be managed supportively such as by using ICP monitors and hyperosmolar therapies [47].

When concurrent with CRS or in early disease, tocilizumab has been efficacious in treating ICANS. As tocilizumab binds to IL-6 receptors, it can paradoxically elevate IL-6 levels in the CNS and potentially worsen ICANS [26]. Unlike tocilizumab, siltuximab directly binds IL-6 directly (while tocilizumab binds the IL-6 receptors) and can be used; however, no direct comparative studies on their individual efficacy have been done. Anakinra, an IL-1 receptor antagonist can play a role in the management of refractory ICANS or HLH in patients treated with axicabtagene ciloleucel [48]. Similarly, there are limited data on the use of IVIG. Another approach is directed at tuning CAR T-cells itself, such as designing inbuilt mechanisms to turn it off in case of severe toxicity [49].

A vast majority of ICANS cases resolve within 3 - 8 weeks [25]. Up to 10% of patients have ongoing symptoms after developing acute ICANS [50]. Long-term sequelae, such as impaired memory and epilepsy have been noted [51].

Immunotherapy in Challenging Populations

ICPIs and CAR T-cell therapies have revolutionized the cancer treatments by enhancing the immune response against cancer cells yet there is a significant restriction in patients who have underlying suppression of immune system as these patients are unable to mount a strong immune reaction against the cancer cells. This poses a significant challenge in clinical decision making by the oncologist in cancer treatment. These challenging conditions include patients with underlying autoimmune conditions, received solid organ or hematological stem cell transplant, chronic viral infections such as human immunodeficiency virus (HIV), hepatitis B and C, and those receiving chronic immunosuppression with high-dose steroids and immunosuppressant. A retrospective study reviewed 30 patients with advanced melanoma with underlying autoimmune conditions including rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus who were treated with ipilimumab. Twenty-seven percent of the patients experienced worsening of autoimmune condition requiring steroid administration [52]. A phase Ib trial evaluated efficacy and safety of ipilimumab in 28 patients with hematological stem cell transplant; 14% of the patients experienced graft-vs-host disease (GVHD) and 21% had irAEs [53]. In the past patients having a chronic viral infection was a near exclusion criteria in immunotherapy trials. Recently, there have been trials evaluating the safety profile of these check point inhibitors in HIV and hepatitis patients. In immunosuppressed patients receiving high-dose steroids or disease-modifying agents for autoimmune diseases, anti PD-1 therapies have been found to be associated with a lower response rate of 15% vs. 44% in patients without immunosuppressant [54]. Therefore, immunotherapy in these patients needs a special consideration and a patient-directed treatment with considering the side effects has to be well thought before starting these therapies.

Conclusions

Recent advances in cancer immunotherapy, especially ICPI and CAR T-cell therapy have shown excellent therapeutic benefits and resulted in increased patient survival rates. However, their use can sometimes be limited due to the accompanying toxicity profile. Both ICPI and CAR T-cell therapy are associated with several neurotoxic effects, most of which are usually manageable if caught early and treated with corticosteroids and other immunosuppressive drugs as needed. However, immunosuppressant use can potentially decrease therapeutic efficacy of these drugs and some cases can be severe and life-threatening. Hence, it is critical to be watchful and have multidisciplinary management of neurological problems.

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Conflict of Interest

There is no conflict of interest of any author in this manuscript.

Author Contributions

Farhan Khalid wrote the introduction and did the literature search. Rajshree Gupta wrote the background of ICPIs. Rajvi Gor wrote the neurological manifestations of the ICPIs. Dairya Gor wrote the background of CAR T-cell therapy. Vinit Singh wrote the neurological toxicity of CAR T-cell therapy. Hussam Eltoukhy was the mentor for the study and helped in the final editing of the manuscript.

Data Availability

This review has focused the literature available on the PubMed and clinical trials. The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

ICPI: immune checkpoint inhibitors; CAR: chimeric antigen receptor; irAEs: immune-related adverse events; ALL: acute lymphoblastic leukemia; DLBCL: diffuse large B-cell lymphoma; CTLA-4: cytotoxic T-lymphocyte antigen-4; PD-1: programmed death 1; APCs: antigen-presenting cells; TCR: T-cell receptor; MHC: major histocompatibility complex; CTCAE: Common Terminology Criteria for Adverse Events; MG: myasthenia gravis; EMG: electromyography; ICU: intensive care unit; IVIG: intravenous immunoglobulin; AIDP: acute inflammatory demyelinating polyneuropathy; CIDP: chronic inflammatory demyelinating polyneuropathy; GBS: Guillain-Barre syndrome; MS: multiple sclerosis; ADL: activities of daily living; CRS: cytokine release syndrome; CRES: CAR T cell-related encephalopathy syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; PRES: posterior reversible encephalopathy syndrome; scFv: single-chain variable fragment; MCP-1: monocyte chemoattractant protein-1; CSF: cerebral spinal fluid; CARTOX: CAR-T-cell therapy-associated-toxicity; ASTCT: American Society for Transplant and Cellular Therapy; ICE: immune effector cell-associated encephalopathy; HLH: hemophagocytic lymphohistiocytosis; BCMA: B-cell maturation antigen; IFN: interferon; TNF: tumor necrosis factor; EEG: electroencephalography; GVHD: graft-vs-host disease

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