Cancer Treatment Reviews 97 (2021) 102189

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Complications of Treatment

Neurological complications of cancer immunotherapy

Patrick Roth [a,*], Sebastian Winklhofer [b], Antonia M.S. Müller [c], Reinhard Dummer [d], Maximilian J. Mair [f], Dorothee Gramatzki [a], Emilie Le Rhun [a,e], Markus G. Manz [c], Michael Weller [a], Matthias Preusser [f]

[a] Department of Neurology & Brain Tumor Center, University Hospital and University of Zurich, Zurich, Switzerland
[b] Department of Neuroradiology, University Hospital and University of Zurich, Zurich, Switzerland
[c] Department of Medical Oncology and Hematology, University Hospital and University of Zurich, Zurich, Switzerland
[d] Department of Dermatology, University Hospital and University of Zurich, Zurich, Switzerland
[e] Department of Neurosurgery, University Hospital and University of Zurich, Zurich, Switzerland
[f] Division of Oncology, Department of Medicine I, Medical University of Vienna, Austria

ARTICLE INFO

Keywords:
Immune checkpoint inhibitor
PD-1
CTLA-4
Neurotoxicity
CNS
Nerve
CAR T cell
Blinatumomab
CD19

ABSTRACT

Immunotherapy has emerged as a powerful therapeutic approach in many areas of clinical oncology and hematology. The approval of ipilimumab, a monoclonal antibody targeting the immune cell receptor CTLA-4, has marked the beginning of the era of immune checkpoint inhibitors. In the meantime, numerous antibodies targeting the PD-1 pathway have expanded the class of clinically approved immune checkpoint inhibitors. Furthermore, novel antibodies directed against other immune checkpoints are currently in clinical evaluation. More recently, bispecific antibodies, which link T cells directly to tumor cells as well as adoptive T cell transfer with immune cells engineered to express a chimeric antigen receptor, have been approved in certain indications. Neurological complications associated with the use of these novel immunotherapeutic concepts have been recognized more and more frequently. Immune checkpoint inhibitors may cause various neurological deficits mainly by alterations of the peripheral nervous system's integrity. These include radiculopathies, neuropathies, myopathies as well as myasthenic syndromes. Side effects involving the central nervous system are less frequent but may result in severe clinical symptoms and syndromes.

The administration of chimeric antigen receptor (CAR) T cell is subject to rigorous patient selection and their use is frequently associated with neurological complications including encephalopathy and seizures, which require immediate action and appropriate therapeutic measures.

Close clinical monitoring for neurological symptoms is key for early recognition of immunotherapy-related side effects. Comprehensive diagnostic work-up and adequate therapeutic measures are essential to avoid further clinical deterioration and residual neurological deficits.

Cancer immunotherapy

Immune checkpoint inhibitors

Background and mode of action

Immune checkpoint inhibitors (ICI) are a group of monoclonal antibodies, which aim at restoring and boosting the anti-tumor activity of cytotoxic T cells. They act by interfering with inhibiting signals, which reduce the activity of T cells. This can be achieved by blocking immune cell receptors expressed on T cells or by binding to the respective ligand, which is present on antigen-presenting or tumor cells. The therapeutic efficacy of this concept has been demonstrated in many clinical trials across various types of cancer [1]. While the field is now dominated by drugs targeting the programmed cell death-1 (PD-1) pathway, the first ICI that obtained clinical approval was ipilimumab, which binds to cytotoxic T-lymphocyte antigen 4 (CTLA-4) and thereby abrogates the inhibiting function of this molecule. Ipilimumab has been approved for the treatment of advanced metastatic melanoma and therefore, most data on its clinical activity but also side effects and toxicity stem from melanoma patients.

An increasing group of drugs target the immune cell receptor PD-1 or its major ligand PD-L1. The latter can be expressed by antigen-

* Corresponding author at: Department of Neurology and Brain Tumor Center, University Hospital Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland.
E-mail address: patrick.roth@usz.ch (P. Roth).

https://doi.org/10.1016/j.ctrv.2021.102189
Received 12 November 2020; Received in revised form 16 March 2021; Accepted 18 March 2021
Available online 23 March 2021

presenting cells as well as tumor cells. Engagement of PD-1 by one of its ligand dampens T cell activity. The administration of drugs targeting either PD-1 or PD-L1 aims at allowing anergic but potentially cancer-targeting T cells to execute their function. PD-1/PD-L1 inhibitors have proven their clinical activity in various types of cancer. Therefore, an increasing use of PD-1/PD-L1 inhibitors has been seen in clinical oncology over the last years. Furthermore, novel drugs targeting other immune checkpoint molecules such as TIGIT, GITR or LAG3 are in clinical development [2]. While these new approaches have yielded promising results in clinical trials, it needs to be awaited which of these drugs will be approved for clinical use.

Complications associated with the use of immune checkpoint inhibitors

Already during early clinical development, various adverse effects attributed to the administration of ICI were observed. While it seems obvious that most, if not all, side effects might be due to overshooting T cell activation, the exact underlying pathophysiological mechanisms remain only partially understood [3]. Furthermore, it remains unclear if there are differences in the immune response in different organs in terms of timing, duration and intensity. ICI-associated side effects, frequently referred to as "immune-related adverse events" (irAE), are considered an inflammatory reaction which is promoted by different factors [4]. These include increasing T cell activity against antigens that are also expressed in healthy tissue [5]. This situation, with T cells recognizing antigens jointly expressed on tumor cells but also healthy tissue, may partially resemble classic paraneoplastic syndromes. Furthermore, checkpoint inhibition may also lead to elevated titers of preexisting autoantibodies which subsequently recognize and target antigens expressed on normal tissue [6]. Increased levels of pro-inflammatory cytokines may play an important role in the development of immune-related toxicities and serve as biomarkers [7]. Finally, activation of the complement system may also drive inflammation [8] (Fig. 1).

Among the organs, which are frequently affected by irAE, are the skin, liver, gastrointestinal tract (mainly colon), different endocrine organs such as the thyroid and pituitary glands, but also lung, kidney, joints and muscles. There is an increasing body of literature suggesting that virtually all organs may be affected by irAE [9]. Overall, complications seem to be more frequent with the use of CTLA-4-targeting

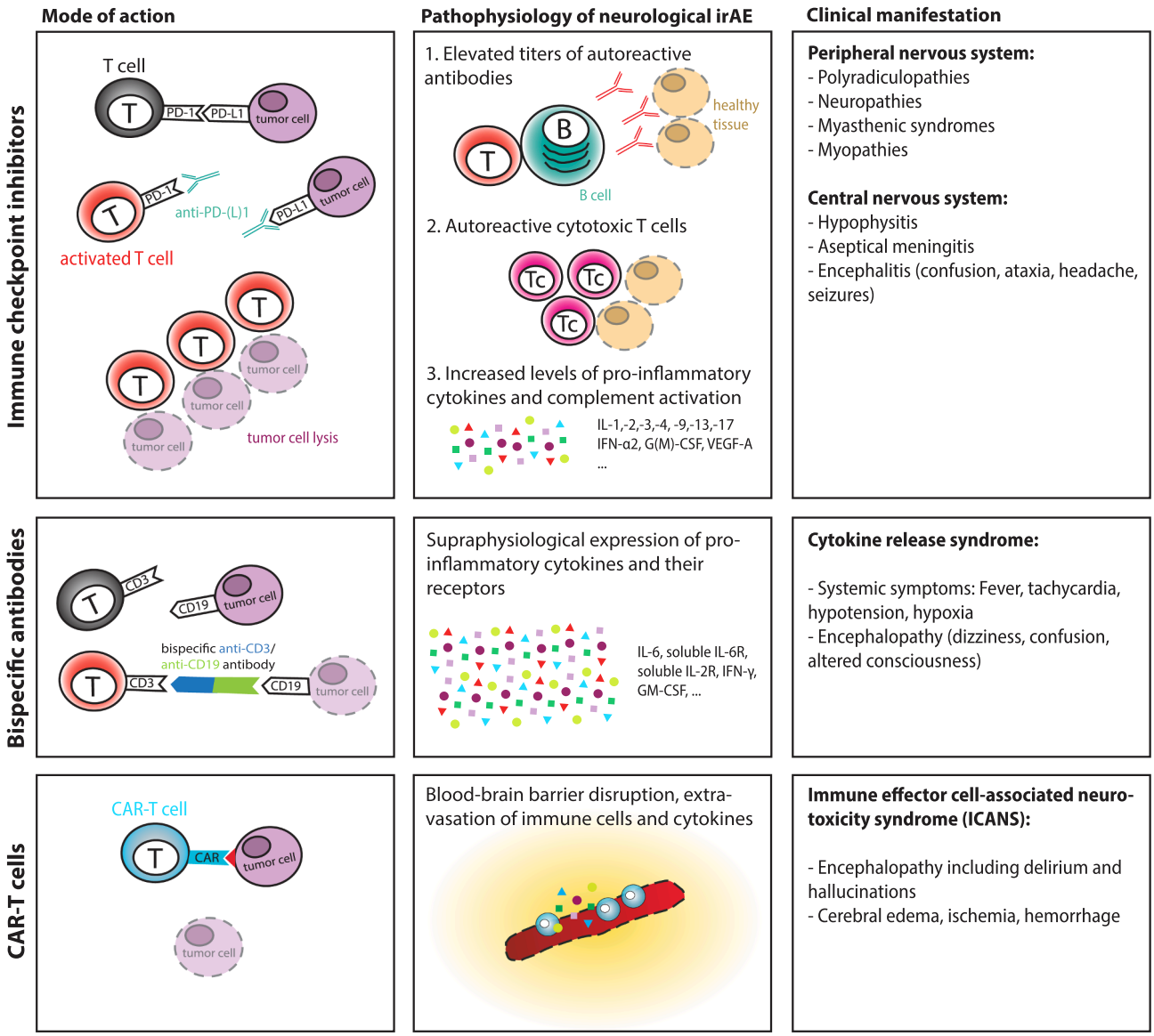

Fig. 1. Pathophysiology of immune-related neurological complications. The presumed mechanisms leading to neurological complications in the context of treatment with ICI, bispecific antibodies and CAR T cells are shown. Abbreviations: IL, interleukin; IFN, interferon; GM-CSF, granulocyte-macrophage colony-stimulating factor; VEGF, vascular endothelial growth factor.

agents compared to drugs, which interfere with the PD-1/PD-L1 axis. Furthermore, the toxicity of the anti-CTLA-4 antibody ipilimumab is dose-dependent with a higher incidence of adverse events observed in patients receiving a dose of 10 mg/kg compared to lower doses [10]. Combined approaches, which interfere with both pathways, have been reported to induce irAE more frequently and more severely compared to either treatment alone [9].

Compared to the frequency of other irAE, e.g., those involving the skin or the gastrointestinal tract, the incidence of neurological complications associated with the use of ICI is rather low (Table 1). It is in the range of 4–6% for monotherapy with anti-CTLA4 and anti-PD1 antibodies, and around 12% for the combination [11]. In an analysis of more

Table 1
Clinical features, incidence, differential diagnosis and clinical work-up of immune-related neurological complications. ICI = immune checkpoint inhibitors, GBS = Guillain-Barré syndrome, CSF = cerebrospinal fluid, MRI = magnetic resonance imaging, IVIG = intravenous immunoglobulins, CK = creatine kinase, CAR = chimeric antigen receptor.

	Clinical features	Incidence	Differential diagnosis	Diagnostic work-up	Management
Peripheral nervous system					
Polyradiculopathies, neuropathies	- Sensory deficits - Motor deficits - Areflexia - Facultative involvement of cranial nerves (may be isolated)	ICI: Overall ~ 1.3%; GBS-like syndrome: 0.1–0.2% [74,75]	- GBS (postinfectious, paraneoplastic cases reported [76] - Chronic inflammatory demyelinating polyneuropathy - Chemotherapy-associated neuropathy	- Electrophysiological work-up - Laboratory diagnostics including CSF: "albuminocytological dissociation" (elevated protein without pleocytosis) may not be present in ICI-related GBS-like syndrome [77] - MRI: contrast-enhancing nerve roots or peripheral nerves	- Steroids - IVIG
Myasthenic syndromes	- Ocular myasthenia: bilateral ptosis, diplopia - Generalized myasthenia: generalized weakness, dysphagia, dyspnea - May be accompanied by myositis, myocarditis	ICI: 0.12–1.16% [74,75]	- Myasthenia gravis	- Acetylcholine receptor autoantibodies in 60% (more frequent in Myasthenia gravis)	- Acetylcholine esterase inhibitors (such as pyridostigmine) - Steroids (risk of initial clinical deterioration) - IVIG - Plasmapheresis
Myopathies	- Muscle pain - Progressive limb weakness (typically proximally accentuated) - Necrotizing autoimmune myositis, dermatomyositis and polymyositis - Cardiac involvement more frequent than in idiopathic dermatomyositis/ polymyositis (up to 30%)	ICI: 0.58–1.67% [74,75]	- Dermatomyositis - Polymyositis	- Laboratory diagnostics: Increased serum CK - Muscle biopsy: lymphocyte infiltration - Electroneuromyography - Cardiological workup if suspected cardiac involvement - Autoantibodies less frequently observed than in dermatomyositis and polymyositis [78]	- Steroids
Central nervous system					
Hypophysitis	- Fatigue - Generalized weakness - Headaches	ICI: 1.00% [75]	- Metastasis - Pituitary apoplexy	- Hormonal diagnostics	- Hormone replacement therapy
Aseptical meningitis	- Neck stiffness - Headache - Fever - Nausea	ICI: 0.36% [75]	- Bacterial/viral meningitis - Neoplastic meningitis	- CSF: lymphocytosis, absence of neoplastic cells/infectious agents - MRI: meningeal contrast enhancement	- Steroids - IVIG - Plasmapheresis
Encephalitis	- Confusion - Fever - Headache - Seizures	ICI: 0.84% [75]	- Paraneoplastic encephalitis - Infectious encephalitis - Metabolic derangement	- Laboratory diagnostics: elevated IL-6 may be seen; exclusion of metabolic etiology - Paraneoplastic autoantibodies: anti-Ma2, anti-Hu, anti-NMDA - CSF: absence of tumor cells or infectious agents - MRI: T2/FLAIR hyperintensities, contrast-enhancing spots	- Steroids - IVIG - Plasmapheresis - Rituximab (anti-CD20)
Cytokine release syndrome (CRS)	- Encephalopathy: Altered consciousness, dizziness, confusion, headache, tremor - Fever, tachycardia, tachypnea, hypotension, hypoxia	blinatumomab: 11–14.2% (≥grade III: 0.8–5%); CAR-T cells: 18–100% (≥grade III: 8–46%) [79]	- Immune effector cell-associated neurotoxicity syndrome (ICANS)	- Elevated serum C-reactive protein, ferritin, IL-6 [80]	- Steroids - Tocilizumab (anti-IL-6R) - Siltuximab (anti-IL-6)
Immune effector cell-associated neurotoxicity syndrome (ICANS)	- Encephalopathy including delirium, hallucinations and seizures - Cerebral edema, ischemia, hemorrhage	CAR-T cells: 21–64% (≥grade III: 12–31%) [81]	- Cytokine release syndrome (CRS)	- EEG: encephalopathic pattern - MRI: unspecific T2/FLAIR hyperintensities	- Steroids - Antiepileptic drugs

than 1′800 patients, the frequency of severe (grade 3–5) neurological adverse events was 2.2% among patients treated with CTLA-4 inhibitors, 1.0% among patients receiving PD-1/PD-L1 inhibitors and 2.8% among patients receiving combined treatment with drugs targeting the PD-1 and CTLA-4 pathways [12]. A series of 649 patients receiving monotherapy with a PD-1 inhibitor reported an incidence of neurological adverse events of 2.6%. Compared to patients who did not experience neurological side effects, no difference was seen for age and sex [13]. Some analyses suggest that neurological irAE are more frequent in patients suffering from melanoma compared to other types of cancer [13,14]. While neurological complications may occur at any time during ICI, their onset is most frequent in the first 3–4 months after treatment initiation. Myasthenic syndromes may occur earlier than other neurological complications [11,14,15].

Diagnostic work-up and differential diagnosis

Despite the well-known side effects of ICI, all patients who present with neurological symptoms require a thorough work-up to exclude other underlying reasons. The lack of well-established diagnostic criteria for immune-related complications has remained a general challenge. While some complications of ICI have been rather well characterized, the diagnosis of an immunotherapy-related complication should only be rendered upon careful exclusion of other possible causes, which may require a different therapeutic management (Table 1). Depending on the clinical presentation of the patient, the cancer diagnosis, comorbidities, cardiovascular risk factors and concomitant medication as well as other reasons must be considered. The list of differential diagnosis therefore comprises tumor progression, e.g., solid tumor manifestations affecting structures of the central or peripheral nervous system as well as tumor cell spread to the cerebrospinal fluid (CSF) compartment, vascular complications such as ischemia or bleeding, metabolic or toxic conditions, infections, epilepsy as well as side effects due to previous or ongoing systemic therapies. Therefore, appropriate diagnostic measures like imaging, CSF diagnostic, electrophysiological assessments such as electroencephalography and electromyoneurography as well as additional laboratory assessments need to be initiated depending on the clinical picture (Table 1). Importantly, only a comprehensive and rapid diagnostic work-up will preclude that treatment with ICI is prematurely and unnecessarily stopped. In contrast, if neurological complications are attributed to immunotherapy, continued treatment can increase the risk of severe and potentially irreversible neurological deficits.

Therapeutic management

Despite the broad use of ICI and the increasing knowledge about incidence, clinical presentation and severity of irAE, there is no generally accepted approach regarding their management. Several guidelines have become available but data from prospective trials are lacking [16]. The situation is even more unsatisfactory for neurological irAE, which were only recognized more recently. Most data and information relies on anecdotal reports and case series. As a general principle, the management of these patients aims at preventing further clinical deterioration and avoiding the manifestation of irreversible neurological deficits. Close clinical monitoring may be sufficient in patients suffering from very mild symptoms. However, there is a general consensus that treatment with ICI should be discontinued rather early in the event of neurological symptoms attributed to this treatment. Furthermore, patients with increasing symptom burden require additional treatment. Here, the administration of steroids, aiming at suppressing the inflammatory immune reaction, is the next therapeutic step. At most centers, intravenous high-dose steroids, e.g., methylprednisolone, are used followed by oral continuation and tapering. Patients who are refractory to this treatment may require even more intense immunosuppressive therapy. Again, no standards have been established in clinical trials and several approaches have been described such as the use of intravenous immunoglobulins or plasmapheresis, treatment with the B cell-depleting antibody rituximab or immunsuppressive drugs such as cyclophosphamide or methotrexate [17,18]. There are anecdotal reports on even more experimental strategies including the use of natalizumab or tacrolimus [19,20]. For some neurological complications, additional therapeutic measures should be evaluated (Table 1). These specific considerations are mentioned in the following section for the corresponding clinical syndromes.

Immune checkpoint-inhibitor-associated complications involving the peripheral nervous system

The majority of neurological irAE affects the peripheral nervous system. Here, basically all anatomical structures may be impaired including nerve root, peripheral nerve, neuromuscular junction, and muscle.

Polyradiculopathies and neuropathies

Among the more frequently reported neurological complications of ICI therapy are clinical symptoms caused by an impairment of the nerve root and/or the peripheral nerve. They have been observed in patients treated with CTLA-4 as well as PD-1/PD-L1 antagonists [21,22]. The clinical spectrum of radiculopathies, neuropathies or the combination, that is, polyradiculoneuropathy (also referred to as Guillain-Barré-like syndrome), is characterized by sensory and/or motor deficits typically affecting the extremities, areflexia as well as impairment of cranial nerves, which mostly present symmetrically. Isolated cranial mononeuropathies have also been observed [23,24]. Neuropathies may present with an affection of small sensory-type fibers or reflect chronic inflammatory demyelinating polyneuropathy. Importantly, the broad spectrum of other pathologies and factors which may underlie the development of (radiculo)neuropathies must be carefully ruled out which typically requires appropriate electrophysiological work-up and laboratory diagnostics, including CSF analysis, as recommended by standard guidelines [25]. “Albuminocytological dissociation”, which is characterized by normal cell count and increased protein levels, has been described in patient suffering from polyradiculitis [26]. MRI can show contrast enhancement of the nerve roots or peripheral nerves (Fig. 2). The administration of steroids may result in clinical improvement. In patients who respond insufficiently, intravenous immunoglobulins (IVIG) or plasmapheresis should be considered [4].

Myasthenic syndromes

The neuro-muscular junction is the anatomical bridge between the peripheral nerve and the muscle. Classical myasthenia gravis is the result of autoantibodies binding to acetylcholine receptors at the presynaptic membrane. There is an increasing number of reports describing myasthenic syndromes in patients being treated with ICI. The clinical picture typically involves bilateral ptosis and diplopia, resembling ocular myasthenia. Generalized myasthenia is characterized by weakness of further muscle groups, dysphagia and dyspnea, even requiring intensive care treatment in some patients.

During treatment with checkpoint inhibitors, most patients have new-onset myasthenia, but aggravation of a pre-existing disorder has also been observed [27]. Myasthenic symptoms were more commonly observed following PD-1 blockade, but anti-CTLA-4 therapy-associated cases were also described and most patients became clinically symptomatic within 6–8 weeks after initiation of immunotherapy [28]. However, only approximately 60% of patients had antibodies to the acetylcholine receptor. Preliminary data suggest that interleukin (IL)-17 may play a role in the development of myasthenic syndromes upon ICI therapy [29]. Importantly, myasthenic syndromes may be accompanied by myositis and myocarditis (see below) [14,30].

Patients suffering from myasthenic syndromes may benefit from the administration of an acetylcholinesterase inhibitor such as pyridostigmine [31]. Similar to classical myasthenia gravis, the additional administration of steroids may be beneficial but poses the risk of a transient clinical deterioration upon treatment initiation. If these

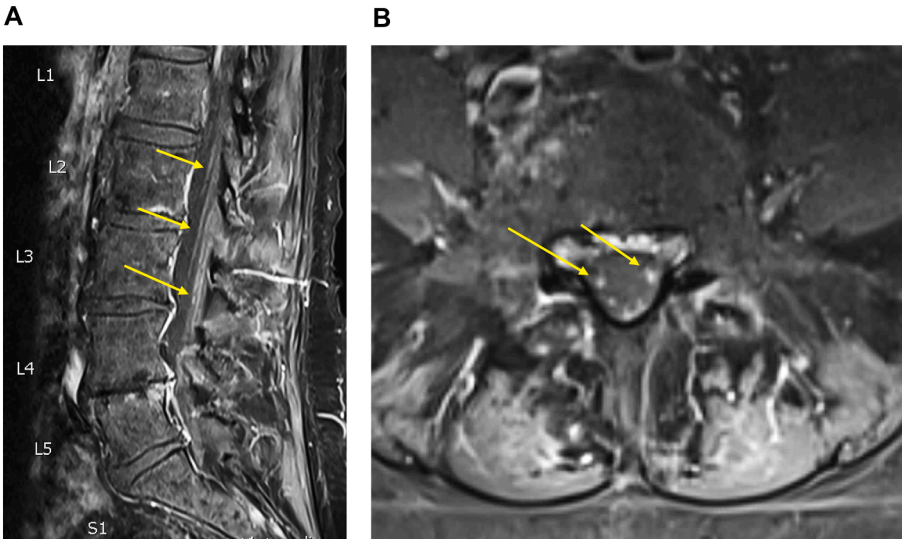

Fig. 2. Immune checkpoint inhibitor-associated polyradiculoneuropathy. Immune checkpoint inhibitor-associated polyradiculopathy in a 77-year-old female patient with a malignant melanoma treated with ipilimumab and nivolumab. Sagittal (A) and axial (B) T1 weighted MRI after intravenous gadolinium application demonstrates contrast enhancement of the nerve roots of the cauda equina (arrows) in the lumbar spine.

approaches are insufficient, IVIG or plasmapheresis can be used as an escalating treatment strategy.

Myopathies

Myopathies belong to the most frequently reported neurological complications associated with the use of ICI. Histological analyses typically demonstrate an infiltration of the muscle tissue with lymphocytes and creatine kinase (CK) levels in the blood are elevated. Necrotizing autoimmune myositis, dermatomyositis and polymyositis have been described [31,32]. Accordingly, patients may also require dermatological and rheumatological evaluations. Most patients complain about muscle pain, which may be accompanied by progressing weakness, typically affecting the proximal limbs. Dysarthria and dysphagia as well as diplopia and ptosis have also been reported [31]. Importantly, ICI-induced myositis may involve the heart in up to 30% of patients [30,33]. Therefore, patients should be examined for possible signs of myocarditis and have cardiological work-up as considered appropriate. Increased serum CK levels may trigger further diagnostics including electroneuromyography, showing myopathic abnormalities, and muscle biopsy. Clinical benefit from steroid therapy has been reported [26,34]. The prognosis is variable but seems to be rather favorable with many patients experiencing full recovery [34].

Immune checkpoint inhibitor-associated complications involving the central nervous system

The central nervous system (CNS) is only rarely affected by side effects due to ICI treatment. However, patients suffering from CNS toxicity may require immediate diagnostic work-up as well as rapid therapeutic measures including management on an intensive care unit, depending on the severity of the clinical symptoms.

Hypophysitis

While CNS complications in the context of ICI treatment are overall rare, hypophysitis has been frequently observed and is well characterized. Anti-CTLA-4 therapy is associated with hypophysitis in approximately 10% of patients and is typically diagnosed 6–8 weeks or later after initiation of therapy [35]. In contrast, it seems much less frequent in patients receiving anti-PD-1/PD-L1 treatment. There is a broad range of largely unspecific symptoms that may occur in patients affected by hypophysitis, including fatigue, muscular weakness, headaches and others [36]. Endocrine work-up includes hormone analyses in the blood and imaging (MRI) to evaluate the function and integrity of the pituitary gland and exclude differential diagnoses such as tumor metastasis or pituitary apoplexy (Fig. 3). Steroids are mostly not beneficial and therapeutic strategies should mainly focus on appropriate hormone replacement [37].

Aseptic meningitis

There are several anecdotal reports on the occurrence of an aseptic meningitis in patients who are on ICI therapy. Meningitis may present with neck stiffness, headache as well as fever and may be accompanied by encephalitis (see below). Sterile CSF with lymphocytosis and imaging demonstrating meningeal contrast enhancement are key diagnostic findings [38].

Encephalitis

Encephalitis is a rare but potentially severe and life-threatening complication and has been described in an increasing number of case reports and small series in patients receiving ipilimumab, PD-1/PD-L1 inhibitors or combinations thereof [39–44]. It may occur within weeks but also months after treatment initiation [23]. In a series of 9 lung cancer patients developing encephalitis upon treatment with PD-1/PD-L1 inhibitors, confusion (78%), fever (45%) and cerebellar ataxia (33%) were the most frequent symptoms but patients also suffered from headache, seizures and other deficits [45]. Three patients required intensive care. All patients but one survived without sequelae. MRI imaging may demonstrate T2/FLAIR hyperintensities and contrast-enhancing spots (Fig. 4) but normal imaging findings do not exclude the diagnosis of an encephalitis. Increased levels of IL-6 and paraneoplastic antibodies such as anti-Ma2, anti-Hu and anti-NMDA have been described [17,39,46]. Diagnostic work-up needs to rule out other underlying pathologies including infections, tumor cell spread to the CSF or brain parenchyma or metabolic alterations. Steroids, intravenous immunoglobulins and plasmapheresis have been applied [47,48]. Beyond these strategies, natalizumab, a drug directed against the α4 integrin, and the CD20-targeting antibody rituximab have been proposed as experimental approaches [17,19].

Other complications in the CNS

Multiple sclerosis is an autoimmune disease, which is characterized by demyelinating lesions in the brain and the myelon and may also

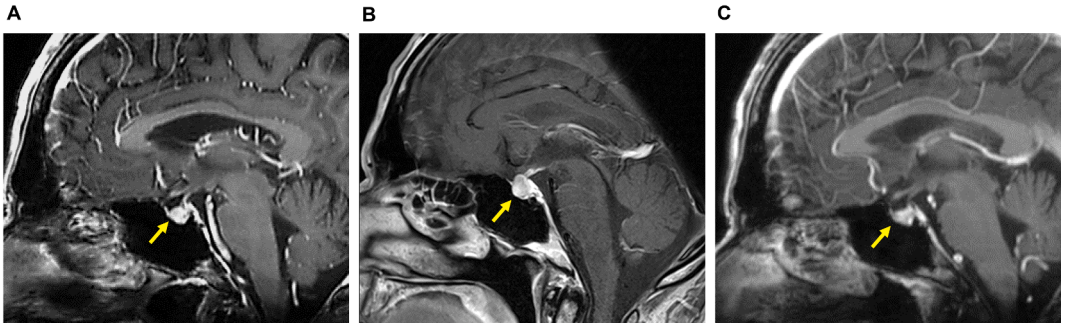

Fig. 3. Hypophysitis following combined treatment with ipilimumab and nivolumab. Immunotherapy-associated hypophysitis in a 66-year-old male patient with a malignant melanoma treated with ipilimumab and nivolumab. Sagittal T1 weighted contrast enhanced MRI demonstrates a normal appearing pituitary gland (arrow) prior to the initiation of immunotherapy (A). After three infusions of ipilimumab and nivolumab, the patient developed headaches and hypopituitarism. Subsequent MRI demonstrated an enlarged and inhomogeneously contrasted pituitary gland (B) extending in the suprasellar cistern. After stopping the medication, the size of the pituitary gland normalized in the MRI four months later (C).

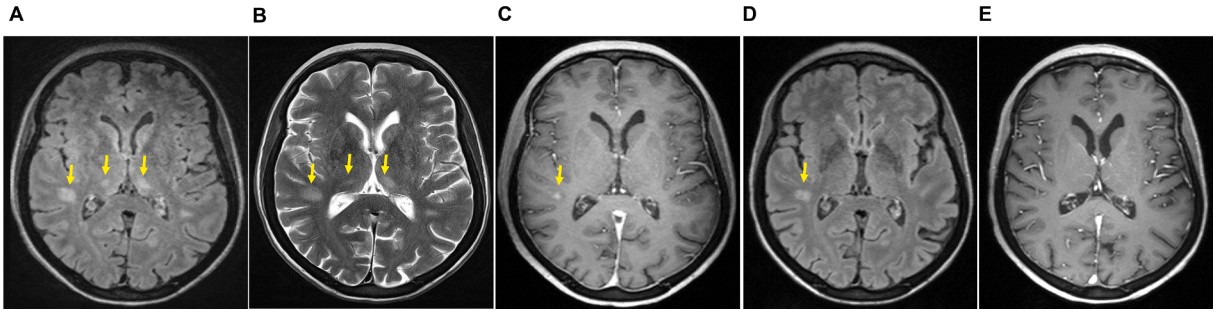

Fig. 4. Nivolumab-associated encephalitis. Encephalitis in a 68-year-old female patient with a malignant melanoma treated with nivolumab. Axial FLAIR (A) and T2 weighted (B) MRI demonstrates bilateral hyperintensities in the thalamus and in the right temporal lobe with associated contrast enhancement in T1 weighted images after gadolinium injection (C, arrows). Follow-up images two months later after stopping immunotherapy demonstrate a size reduction of the right temporal FLAIR lesion with vanished thalamic lesions (D, arrow) and vanished contrast enhancement in T1 images after gadolinium (E).

involve the optic nerve. Patients with known multiple sclerosis may experience more frequent and severe relapse under the influence of ICI [49]. Furthermore, newly diagnosed CNS demyelination has been described in patients receiving ICI therapy [50,51]. While the causal relationship remains poorly understood, the mechanism of action of ICI may be associated with increased inflammation and subsequent demyelination.

Furthermore, there is an increasing number of anecdotal reports on additional neurological complications in the context of ICI therapy. This includes patients with a diagnosis of neurosarcoidosis or CNS vasculitis [52–54]. Because of the rarity of these events, the analysis of larger datasets needs to be awaited to clarify if there is more than co-incidence but rather a direct link between cancer immunotherapy and these CNS complications.

Immune checkpoint inhibitors in the context of brain tumors

Questions have been raised if ICI may be associated with an increased risk of complications in the CNS in patients suffering from a brain tumor. Accordingly, and similar to the development of many other drugs, patients with primary or secondary brain tumors were not eligible in early trials exploring the activity of ICI because of the fear that these patients may be more prone to neurological complications [55]. In the meantime, both CTLA-4 and mainly PD-1 inhibitors were assessed in patients with brain metastases as well as primary brain tumors such as glioblastoma. While there were encouraging findings regarding the clinical activity of these drugs against brain metastasis [56], the results in patients with glioblastoma have remained disappointing [57]. Treatment with checkpoint inhibitors was typically well tolerated and the safety and toxicity profile was comparable to patients with cancer outside the CNS. A retrospective series identified intracranial lesions at the start of PD-1 therapy as a factor associated with a higher rate of neurological complications [13]. However, in most larger trials, no additional neurotoxicity was observed in patients with brain tumors. While continued awareness is mandatory, there are so far no specific concerns regarding the safety and neurological tolerability of ICI in patients with brain tumors, which allows further clinical investigation in these patients [58].

Bispecific antibodies

Background and mode of action

Bispecific constructs represent a novel class of antibody therapeutics in the field of immunotherapy. The term bispecific refers to 2 binding domains which recognize different target antigens. Typically, bispecific antibodies bind to an antigen, which is specifically expressed on a tumor cell and CD3 on T cells by another domain. Hence, the idea of such T cell-redirecting bispecific antibodies (TRBA) is to activate T cells and bring them in close proximity to a tumor cell, thereby allowing for immediate tumor cell killing [59]. While several bispecific antibodies have been explored at the preclinical level, only blinatumomab has been clinically approved in patients with refractory B cell acute lymphoblastic leukemia. Blinatumomab binds to the CD19 antigen on B cells and has a CD3-targeting moiety. Various bispecific constructs are currently in preclinical and clinical development. Depending on the tumor type, these agents target different antigens including HER2, PD-1 or PD-L1, but also other immune checkpoint molecules, mainly aiming at interfering with negative T cell regulation.

Side effects and complications

In contrast to ICI with many clinically approved drugs and

increasingly broad use against different types of cancer, data on adverse effects related to TRBA are largely limited to blinatumomab, the only approved agent. Complications associated with the administration of blinatumomab comprise the development of a cytokine release syndrome (CRS), a systemic inflammatory response, which has been characterized in more detail in the context of CAR T cell therapy (see below). Neurotoxicity may occur in parallel or independent of CRS and partially rely on blinatumomab-induced adhesion of T cells to endothelial cells [60] (Fig. 1). In an analysis of 98 patients suffering from neurological complications related to blinatumomab administration, encephalopathy with altered consciousness, confusion, dizziness, headache and tremor were most frequently diagnosed [61]. Elderly patients were more often affected by neurological symptoms, which typically developed within the first 2 weeks after initiation of treatment. The majority of patients had rather mild neurological symptoms. Stopping blinatumomab therapy and additional administration of steroids has been proposed as a therapeutic approach but further investigations are required to develop the best therapeutic strategy also with respect to the more frequent use of blinatumomab and similar constructs in the future [62].

Adoptive T cell therapy

Background on CAR T cells

Using patient-derived T cells for anti-tumor therapy has long been regarded a promising approach. However, classical concepts such as *ex vivo* expansion and stimulation prior to re-administration did not achieve clinically meaningful anti-tumor activity. This has considerably changed with the concept of T cells that are genetically engineered to express a chimeric antigen receptor (CAR). The CAR consists of an extracellular antigen-binding domain, allowing for binding to a tumor cell, as well as intracellular signaling domains which result in immediate T cell activation upon antigen recognition [63,64]. The treatment of patients with hematological malignancies, particularly B cell neoplasias, using CD19-specific CAR T cells resulted in convincing clinical benefit [65,66]. As a consequence, tisagenlecleucel (Kymriah ®) and axicabtagene-ciloleucel (Yescarta ®) have been the first clinically approved CAR T cell therapies. While this treatment is more and more frequently used against hematological malignancies in clinical routine, it needs to be awaited if this approach will also work against solid tumors.

Side effects associated with the use of CAR T cells

Administration of CAR T cells may result in striking therapeutic activity resulting in long-lasting remissions in many patients. However, the effect of this therapy comes at a price. The administration of genetically engineered T cells, ready to become immediately activated upon antigen recognition may result in several undesired effects. Among these, cytokine release syndrome (CRS) has been increasingly well understood and characterized. CAR T cells may continue to proliferate upon administration to the patient. As suggested by its name, CRS is the result of a supraphysiological expression of various inflammatory cytokines and their corresponding receptors including, but probably not limited to, IL-6 and soluble IL-6 receptor, soluble IL-2 receptor, interferon (IFN)-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Furthermore, upon engagement of other (bystander) immune cells, additional inflammatory cytokines may be secreted at high levels contributing to systemic inflammation. The American Society of Blood and Marrow Transplantation (ASBMT) has developed a score that allows CRS grading using 3 parameters: fever, hypotension and hypoxia [67]. While mild CRS refers to grade 1, more severe manifestations are classified as grade 2, 3 or 4.

CRS can manifest shortly, within days, after CAR T cell administration and is characterized by fever, tachycardia, tachypnoea, arterial hypotension and hypoxia with subsequent organ failure. Patient with CRS typically have increased serum levels of IL-6. Tocilizumab, a monoclonal antibody interfering with IL-6 signaling by blocking the IL-6 receptor (IL-6R) has become a standard treatment in addition to the administration of steroids [68]. Other drugs which interfere with the IL-6 signaling axis, e.g., siltuximab, which binds to IL-6, may also be considered.

While the detailed description and management of CRS is beyond the scope of this article and has been described elsewhere [69], it is important to understand that the pathophysiology of CRS is only partially overlapping with that of neurotoxicity, which is covered in the following section.

CAR T cell-associated neurotoxicity

Neurotoxicity was recognized as a frequent and major complication in patients receiving CAR T cell therapy. Neurological complications related to CAR T cells therapy are summarized under the term immune effector cell-associated neurotoxicity syndrome (ICANS). About 50% of patients receiving CAR T cell therapy develop ICANS [70]. Typically, there is a rather narrow time window associated with the occurrence of CAR T cell-related neurotoxicity, starting around day 3 after T cell infusion and lasting until about 2 weeks later but a delayed onset of neurological complications is also possible. The diagnosis of ICANS may be more challenging in patients also suffering from CRS as both conditions may overlap in time and the symptoms of global encephalopathy may be similarly observed within high fevers with or without CRS, particularly in frail and elderly patients. Unlike CRS, endothelial activation and a disruption of the blood-brain barrier integrity have been proposed as the underlying pathophysiological mechanism leading to the development of ICANS following the administration of CD19-specific CAR T cells [71,73]. Blood-brain barrier disruption may result in cerebral edema and further complications such as tissue ischemia and hemorrhage (Fig. 1). So far, no clear association between the grade of neurotoxicity and the lymphocyte cell count or CAR T cell quantity in the CSF has been found but increased levels of proinflammatory cytokines in the CSF were observed [72].

ICANS typically presents as an encephalopathic condition which involves altered consciousness, confusion, delirium and hallucinations. Some patients suffer from seizures, aphasia, myoclonus and other focal deficits. In severe cases, patients develop coma. Of the few cases of death due to CAR T cell treatment approximately 50% were due to neurotoxicity, specifically cerebral edema. EEG findings are unspecific but are frequently in line with encephalopathy. As with complications due to other immunotherapeutic approaches, other causes that could explain the neurological condition must be ruled out with an appropriate diagnostic work-up. MRI of the brain may be normal in patients suffering from mild symptoms and may show unspecific T2/FLAIR hyperintensities in various regions as well as generalized edema in severe cases [71,72].

The CARTOX-10 score allows for a grading of neurological complications associated with the administration of CAR T cells. It assigns points for questions related to orientation, the naming of 3 objects, writing of a standard sentence and the ability to count backwards from 100 by 10. Depending on the total number of points, ICANS is classified from grade 1 to 5 [69]. A slightly modified version of the CARTOX-10 score has been proposed as Immune Effector Cell-Associated Encephalopathy (ICE) score by the American Society for Transplantation and Cellular Therapy (ASTCT) [67]. Here, a command-following assessment was integrated instead of one of the orientation-related questions of CARTOX-10. About one third of the patients receiving axicabtagene-ciloleucel develop ICANS $\geq$ grade 3 whereas treatment with tisagenlecleucel seems to be less likely associated with severe ICANS [70].

Treatment of ICANS has only been partially established so far. Steroids remain the therapeutic mainstay whereas IL-6R blockade with tocilizumab has no beneficial effect in most patients [68,72]. The lacking benefit from anti-IL-6R antibody therapy is most likely explained by the different pathophysiology of ICANS compared to CRS. Supportive therapy includes antiepileptic medication in patients suffering from seizures or with EEG patterns associated with increased seizure risk.

Newer generation antiepileptic drugs with low interaction potential may be preferred. Particular attention and monitoring is required in patients with a history of neurological problems prior to the initiation of CAR T cell therapy.

Conclusion and outlook

The last decade has seen the raise of several immunotherapeutic strategies in the field of clinical oncology. The number of patients who are undergoing any of these treatments, is continuously increasing. This holds particularly true for the use of ICI where the approval for different cancer entities is continuously expanding. Drugs which act beyond the CTLA-4 or PD1/PD-L1 axis are in late-stage clinical development and may enter regular clinical use in the near future. Therefore, it can be anticipated that the number of patients affected by neurological complications will further increase. Similarly, treatments which are currently restricted to selected patients such as TRBA constructs or CAR T cells will become available at more and more sites and their approval may be expanded to additional cancer indications. Therefore, awareness for neurological irAE, patient education before treatment initiation, close clinical monitoring as well as early and accurate diagnosis is key to initiate appropriate therapeutic measures and to avoid persisting clinical deficits. In line with this, more information, ideally from prospective trials, is required to define therapeutic escalation strategies in patients who respond insufficiently to steroids.

More data are also needed regarding the occurrence of neurological complications and their potential association with response rates and survival. While some preliminary data suggest that such an association exists, analyses of larger datasets are required to support or reject this hypothesis [11]. Furthermore, an improved understanding of possible clinical or laboratory (bio)markers which may help identifying patients who are prone for neurological complications in the context of immunotherapy would be desirable to guide and improve patient management. Finally, until data that are more robust become available, re-initiation of immunotherapy after recovery from a neurological irAE must be decided on an individual basis.

Declaration of Competing Interest

ELR has received honoraria for lectures or advisory board from Tocagen, Abbvie, Daiichy Sankyo.

MP has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen.

PR has received research grants from MSD and Novocure and honoraria for advisory board participation or lectures from Bristol-Myers Squibb, Covagen, Debiopharm, Medac, MSD, Novartis, Novocure, QED, Roche and Virometix.

MW has received research grants from Abbvie, Adastra, Dracen, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, OGD2, Piqur and Roche, and honoraria for lectures or advisory board participation or consulting from Abbvie, Basilea, Bristol Meyer Squibb, Celgene, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Orbus, Roche and Tocagen.

References

[1] Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. Nat Commun 2020;11:3801.

[2] Mazzarella L, Duso BA, Trapani D, Belli C, D'Amico P, Ferraro E, et al. The evolving landscape of 'next-generation' immune checkpoint inhibitors: A review. Eur J Cancer 2019;117:14–31.

[3] Burke KP, Grebinoski S, Sharpe AH, Vignali DAA. Understanding adverse events of immunotherapy: A mechanistic perspective. J Exp Med 2021:218.

[4] Harrison RA, Tummala S, de Groot J. Neurologic Toxicities of Cancer Immunotherapies: a Review. Curr Neurol Neurosci Rep 2020;20:27.

[5] Khan Z, Hammer C, Guardino E, Chandler GS, Albert ML. Mechanisms of immune-related adverse events associated with immune checkpoint blockade: using germline genetics to develop a personalized approach. Genome Med 2019;11:39.

[6] Graus F, Dalmau J. Paraneoplastic neurological syndromes in the era of immune-checkpoint inhibitors. Nat Rev Clin Oncol 2019;16:535–48.

[7] Lim SY, Lee JH, Gide TN, Menzies AM, Guminski A, Carlino MS, et al. Circulating Cytokines Predict Immune-Related Toxicity in Melanoma Patients Receiving Anti-PD-1-Based Immunotherapy. Clin Cancer Res 2019;25:1557–63.

[8] Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med 2018;378:158–68.

[9] Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol 2019;16:563–80.

[10] Guo CY, Jiang SC, Kuang YK, Hu H. Incidence of Ipilimumab-Related Serious Adverse Events in Patients with Advanced Cancer: A Meta-Analysis. J Cancer 2019;10:120–30.

[11] Cuzzubbo S, Javeri F, Tissier M, Roumi A, Barlog C, Doridam J, et al. Neurological adverse events associated with immune checkpoint inhibitors: Review of the literature. Eur J Cancer 2017;73:1–8.

[12] Dubey D, David WS, Reynolds KL, Chute DF, Clement NF, Cohen JV, et al. Severe Neurological Toxicity of Immune Checkpoint Inhibitors: Growing Spectrum. Ann Neurol 2020;87:659–69.

[13] Shi S, Jaoube JA, Kanwar R, Jin MC, Amorin A, Varanasi V, et al. Neurological adverse effects due to programmed death 1 (PD-1) inhibitors. J Neurooncol 2020;148:291–7.

[14] Kao JC, Liao B, Markovic SN, Klein CJ, Naddaf E, Staff NP, et al. Neurological Complications Associated With Anti-Programmed Death 1 (PD-1) Antibodies. JAMA neurology 2017;74:1216–22.

[15] Johnson DB, Manouchehri A, Haugh AM, Quach HT, Balko JM, Lebrun-Vignes B, et al. Neurologic toxicity associated with immune checkpoint inhibitors: a pharmacovigilance study. J Immunother Cancer 2019;7:134.

[16] Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28 Suppl 4. iv119-iv42.

[17] Vogrig A, Muniz-Castrillo S, Joubert B, Picard G, Rogemond V, Marchal C, et al. Central nervous system complications associated with immune checkpoint inhibitors. J Neurol Neurosurg Psychiatry 2020;91:772–8.

[18] Anderson D, Beecher G, Nathoo N, Smylie M, McCombe JA, Walker J, et al. Proposed diagnostic and treatment paradigm for high-grade neurological complications of immune checkpoint inhibitors. Neurooncol Pract 2019;6:340–5.

[19] Hottinger AF, de Micheli R, Guido V, Karampera A, Hagmann P, Du Pasquier R. Natalizumab may control immune checkpoint inhibitor-induced limbic encephalitis. Neurol Neuroimmunol Neuroinflamm 2018;5:e439.

[20] Gaudy-Marqueste C, Monestier S, Franques J, Cantais E, Richard MA, Grob JJ. A severe case of ipilimumab-induced guillain-barre syndrome revealed by an occlusive enteric neuropathy: a differential diagnosis for ipilimumab-induced colitis. J Immunother 2013;36:77–8.

[21] Wilgenhof S, Neyns B. Anti-CTLA-4 antibody-induced Guillain-Barre syndrome in a melanoma patient. Ann Oncol 2011;22:991–3.

[22] Dubey D, David WS, Amato AA, Reynolds KL, Clement NF, Chute DF, et al. Varied phenotypes and management of immune checkpoint inhibitor-associated neuropathies. Neurology 2019;93:e1093–103.

[23] Larkin J, Chmielowski B, Lao CD, Hodi FS, Sharfman W, Weber J, et al. Neurologic Serious Adverse Events Associated with Nivolumab Plus Ipilimumab or Nivolumab Alone in Advanced Melanoma, Including a Case Series of Encephalitis. Oncologist 2017;22:709–18.

[24] Supakornnumporn S, Katirji B. Guillain-Barre Syndrome Triggered by Immune Checkpoint Inhibitors: A Case Report and Literature Review. J Clin Neuromuscul Dis 2017;19:80–3.

[25] Watson JC, Dyck PJ. Peripheral Neuropathy: A Practical Approach to Diagnosis and Symptom Management. Mayo Clin Proc 2015;90:940–51.

[26] Bruna J, Argyriou AA, Anastopoulou GG, Alemany M, Nadal E, Kalofonou F, et al. Incidence and characteristics of neurotoxicity in immune checkpoint inhibitors with focus on neuromuscular events: Experience beyond the clinical trials. J Peripher Nerv Syst 2020;25:171–7.

[27] Lau KH, Kumar A, Yang IH, Nowak RJ. Exacerbation of myasthenia gravis in a patient with melanoma treated with pembrolizumab. Muscle Nerve 2016;54:157–61.

[28] Makarious D, Horwood K, Coward JIG. Myasthenia gravis: An emerging toxicity of immune checkpoint inhibitors. Eur J Cancer 2017;82:128–36.

[29] Mazzarella L, Giugliano S, D'Amico P, Belli C, Duso BA, Rescigno M, et al. Evidence for interleukin 17 involvement in severe immune-related neuroendocrine toxicity. Eur J Cancer 2020;141:218–24.

[30] Johansen A, Christensen SJ, Scheie D, Hojgaard JLS, Kondziella D. Neuromuscular adverse events associated with anti-PD-1 monoclonal antibodies: Systematic review. Neurology 2019;92:663–74.

[31] Moreira A, Loquai C, Pfohler C, Kahler KC, Knauss S, Heppt MV, et al. Myositis and neuromuscular side-effects induced by immune checkpoint inhibitors. Eur J Cancer 2019;106:12–23.

[32] Cappelli LC, Gutierrez AK, Bingham 3rd CO, Shah AA. Rheumatic and Musculoskeletal Immune-Related Adverse Events Due to Immune Checkpoint Inhibitors: A Systematic Review of the Literature. Arthritis Care Res (Hoboken) 2017;69:1751–63.

[33] Zimmer L, Goldinger SM, Hofmann L, Loquai C, Ugurel S, Thomas I, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer 2016;60:210–25.
[34] Psimaras D, Velasco R, Birzu C, Tamburin S, Lustberg M, Bruna J, et al. Immune checkpoint inhibitors-induced neuromuscular toxicity: From pathogenesis to treatment. J Peripher Nerv Syst 2019;24(Suppl 2):S74–85.
[35] Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30:2691–7.
[36] Sznol M, Postow MA, Davies MJ, Pavlick AC, Plimack ER, Shaheen M, et al. Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management. Cancer Treat Rev 2017;58:70–6.
[37] Min L, Hodi FS, Giobbie-Hurder A, Ott PA, Luke JJ, Donahue H, et al. Systemic high-dose corticosteroid treatment does not improve the outcome of ipilimumab-related hypophysitis: a retrospective cohort study. Clin Cancer Res 2015;21:749–55.
[38] Dalakas MC. Neurological complications of immune checkpoint inhibitors: what happens when you 'take the brakes off' the immune system. Ther Adv Neurol Disord 2018;11. 1756286418799864.
[39] Yamaguchi Y, Nagasawa H, Katagiri Y, Wada M. Atezolizumab-associated encephalitis in metastatic lung adenocarcinoma: a case report. J Med Case Rep 2020;14:88.
[40] Bossart S, Thurneysen S, Rushing E, Frontzek K, Leske H, Mihic-Probst D, et al. Case Report: Encephalitis, with Brainstem Involvement, Following Checkpoint Inhibitor Therapy in Metastatic Melanoma. Oncologist 2017;22:749–53.
[41] Robert L, Langner-Lemercier S, Angibaud A, Sale A, Thepault F, Corre R, et al. Immune-related Encephalitis in Two Patients Treated With Immune Checkpoint Inhibitor. Clinical Lung Cancer 2020.
[42] Cabral G, Ladeira F, Gil N. Nivolumab-induced seronegative encephalitis. J Neuroimmunol 2020;347:577350.
[43] Vogrig A, Muniz-Castrillo S, Desestret V, Joubert B, Honnorat J. Pathophysiology of paraneoplastic and autoimmune encephalitis: genes, infections, and checkpoint inhibitors. Ther Adv Neurol Disord 2020;13. 1756286420932797.
[44] Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother 2010;33:828–33.
[45] Sanchis-Borja M, Ricordel C, Chiappa AM, Hureaux J, Odier L, Jeannin G, et al. Encephalitis related to immunotherapy for lung cancer: Analysis of a multicenter cohort. Lung Cancer 2020;143:36–9.
[46] Kang K, Zheng K, Zhang Y. Paraneoplastic Encephalitis and Enteric Neuropathy Associated With Anti-Hu Antibody in a Patient Following Immune-checkpoint Inhibitor Therapy. J Immunother 2020;43:165–8.
[47] Chung M, Jaffer M, Verma N, Mokhtari S, Ramsakal A, Peguero E. Immune checkpoint inhibitor induced anti-glutamic acid decarboxylase 65 (Anti-GAD 65) limbic encephalitis responsive to intravenous immunoglobulin and plasma exchange. J Neurol 2020;267:1023–5.
[48] Kim A, Keam B, Cheun H, Lee ST, Gook HS, Han MK. Immune-Checkpoint-Inhibitor-Induced Severe Autoimmune Encephalitis Treated by Steroid and Intravenous Immunoglobulin. J Clin Neurol 2019;15:259–61.
[49] Gettings EJ, Hackett CT, Scott TF. Severe relapse in a multiple sclerosis patient associated with ipilimumab treatment of melanoma. Mult Scler 2015;21:670.
[50] Pillonel V, Dunet V, Hottinger AF, Berthod G, Schiappacasse L, Peters S, et al. Multiple nivolumab-induced CNS demyelination with spontaneous resolution in an asymptomatic metastatic melanoma patient. J Immunother Cancer 2019;7:336.
[51] Cao Y, Nylander A, Ramanan S, Goods BA, Ponath G, Zabad R, et al. CNS demyelination and enhanced myelin-reactive responses after ipilimumab treatment. Neurology 2016;86:1553–6.
[52] Dunn-Pirio AM, Shah S, Eckstein C. Neurosarcoidosis following Immune Checkpoint Inhibition. Case Rep Oncol 2018;11:521–6.
[53] Tan I, Malinzak M, Salama AKS. Delayed onset of neurosarcoidosis after concurrent ipilimumab/nivolumab therapy. J Immunother Cancer 2018;6:77.
[54] Laubli H, Hench J, Stanczak M, Heijnen I, Papachristofilou A, Frank S, et al. Cerebral vasculitis mimicking intracranial metastatic progression of lung cancer during PD-1 blockade. J Immunother Cancer 2017;5:46.
[55] Roth P, Pace A, Le Rhun E, Weller M, Ay C, Cohen-Jonathan Moyal E, et al. Neurological and vascular complications of primary and secondary brain tumours: EANO-ESMO Clinical Practice Guidelines for prophylaxis, diagnosis, treatment and follow-up. Ann Oncol 2021;32:171–82.
[56] Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. N Engl J Med 2018;379:722–30.
[57] Reardon DA, Brandes AA, Omuro A, Mulholland P, Lim M, Wick A, et al. Effect of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma: The CheckMate 143 Phase 3 Randomized Clinical Trial. JAMA Oncol 2020;6:1003–10.
[58] Wen PY, Weller M, Lee EQ, Alexander BA, Barnholtz-Sloan JS, Barthel FP, et al. Glioblastoma in Adults: A Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) Consensus Review on Current Management and Future Directions. Neuro Oncol 2020;22(8):1073–113.
[59] Goebeler ME, Bargou RC. T cell-engaging therapies - BiTEs and beyond. Nat Rev Clin Oncol 2020;17:418–34.
[60] Klinger M, Zugmaier G, Nagele V, Goebeler ME, Brandl C, Stelljes M, et al. Adhesion of T Cells to Endothelial Cells Facilitates Blinatumomab-Associated Neurologic Adverse Events. Cancer Res 2020;80:91–101.
[61] Stein AS, Schiller G, Benjamin R, Jia C, Zhang A, Zhu M, et al. Neurologic adverse events in patients with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab: management and mitigating factors. Ann Hematol 2019;98:159–67.
[62] Jain T, Litzow MR. No free rides: management of toxicities of novel immunotherapies in ALL, including financial. Blood Adv 2018;2:3393–403.
[63] Dai H, Wang Y, Lu X, Han W. Chimeric Antigen Receptors Modified T-Cells for Cancer Therapy. J Natl Cancer Inst 2016;108.
[64] June CH, Sadelain M. Chimeric Antigen Receptor Therapy. N Engl J Med 2018;379:64–73.
[65] Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507–17.
[66] Porter D, Frey N, Wood PA, Weng Y, Grupp SA. Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel. J Hematol Oncol 2018;11:35.
[67] Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2019;25:625–38.
[68] Schmidts A, Wehrli M, Maus MV. Toward Better Understanding and Management of CAR-T Cell-Associated Toxicity. Annu Rev Med 2020.
[69] Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol 2018;15:47–62.
[70] Pennisi M, Jain T, Santomasso BD, Mead E, Wudhikarn K, Silverberg ML, et al. Comparing CAR T-cell toxicity grading systems: application of the ASTCT grading system and implications for management. Blood Adv 2020;4:676–86.
[71] Gust J, Hay KA, Hanafi LA, Li D, Myerson D, Gonzalez-Cuyar LF, et al. Endothelial Activation and Blood-Brain Barrier Disruption in Neurotoxicity after Adoptive Immunotherapy with CD19 CAR-T Cells. Cancer Discovery 2017;7:1404–19.
[72] Santomasso BD, Park JH, Salloum D, Riviere I, Flynn J, Mead E, et al. Clinical and Biological Correlates of Neurotoxicity Associated with CAR T-cell Therapy in Patients with B-cell Acute Lymphoblastic Leukemia. Cancer Discovery 2018;8:958–71.
[73] Parker KR, Migliorini D, Perkey E, Yost KE, Bhaduri A, Bagga P, Haris M, Wilson NE, Liu F, Gabunia K, Scholler J, Montine TJ, Bhoj VG, Reddy R, Mohan S, Maillard I, Kriegstein AR, June CH, Chang HY, Posey Jr AD, Satpathy AT. Single-Cell Analyses Identify Brain Mural Cells Expressing CD19 as Potential Off-Tumor Targets for CAR-T Immunotherapies. Cell 2020;183(1):126–142.e17. https://doi.org/10.1016/j.cell.2020.08.022.
[74] Kao JC, Brickshawana A, Liewluck T. Neuromuscular Complications of Programmed Cell Death-1 (PD-1) Inhibitors. Curr Neurol Neurosci Rep 2018;18:1–9. https://doi.org/10.1007/s11910-018-0878-7.
[75] Sato K, Mano T, Iwata A, Toda T. Neurological and related adverse events in immune checkpoint inhibitors: a pharmacovigilance study from the Japanese Adverse Drug Event Report database. J Neurooncol 2019;145:1–9. https://doi.org/10.1007/s11060-019-03273-1.
[76] Koike H, Sobue G. Paraneoplastic neuropathy. vol. 115. 1st ed. Elsevier B.V.; 2013. https://doi.org/10.1016/B978-0-444-52902-2.00041-2.
[77] Kolb NA, Trevino CR, Waheed W, Sobhani F, Landry KK, Thomas AA, et al. Neuromuscular complications of immune checkpoint inhibitor therapy. Muscle Nerve 2018;58:10–22. https://doi.org/10.1002/mus.26070.
[78] Moreira A, Loquai C, Pföhler C, Kähler KC, Knauss S, Heppt MV, et al. Myositis and neuromuscular side-effects induced by immune checkpoint inhibitors. Eur J Cancer 2019;106:12–23. https://doi.org/10.1016/j.ejca.2018.09.033.
[79] Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, et al. Cytokine release syndrome. J Immunother Cancer 2018;6. https://doi.org/10.1186/s40425-018-0343-9.
[80] Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323–35. https://doi.org/10.2147/TCRM.S150524.
[81] Neill L, Rees J, Roddie C. Neurotoxicity - CAR T-cell therapy: What the neurologist needs to know. Pract Neurol 2020;20:287–95. https://doi.org/10.1136/practneurol-2020-002550.