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Navigating the Neurological Adverse Effects of Cancer Immunotherapy: Challenges and Opportunities.

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Abstract

The development of cancer immunotherapy has redefined how cancer is treated and further, patients will employ immunotherapy to cure cancer by targeting cancerous cells. Nevertheless, neural irAEs have also appeared as this new line of defense; a result of this novel treatment approach. The goal of this narrative review is to present a comprehensive overview of cancer immunotherapy with an emphasis on immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) T-cell-based therapies, and bispecific T-cell engagers (BiTEs), including description of the adverse neurological consequences related to these cancer immunotherapies. Electronic databases such as PubMed, Google Scholar, and Web of Science as well as qualitative synthesis of literature were used to conduct the literature search and synthesis of the literature. Neurological irAEs may involve the: peripheral nervous system, (PNS), the central nervous system (CNS), the neuromuscular junction, and the autonomic nervous system. The occurrence and the timing of these complications is different based on type of immunotherapy and personal risk factors. Pathophysiology Immune dysregulation, autoimmunity and neuroinflammation are believed to contribute to the pathophysiology of neurological irAEs. They also have heterogeneous clinical presentations which may complicate diagnosis and may overlap with other conditions. Treatments options comprise withdrawals of immunotherapy and immunosuppressive therapy with corticosteroids as well as further immunomodulatory agents, in severe or defiant cases. Oncologists, neurologists, and other medical workers should collaborate on multidisciplinary terms to provide the highest quality of assistance to the patient. All the patients have full recovery, but some patients develop persistent neurological deficits or even die. Future studies need to be directed to clarify the working mechanisms, determine prescriptive markers, and evidence-based treatment guidelines to

enhance patient safety and outcome. With the future of cancer immunotherapy shaping up, there has been a need to better understand the associated neurological complications in order to treat patients and further the potential of the entire field.

Keywords: Immunotherapy, Immune-related adverse events (irAEs), Neurotoxicity, Cancer treatment, Adverse effects.

Introduction:

Neurological complications in cancer immunotherapy is a recent and more recognized phenomena in the newly evolving field of cancer treatment. Conventional cancer treatments, including chemotherapy and radiation, work mostly through attacking rapid dividing cells, and their side effects are more or less well understood (1). Conversely, the emergence of immunotherapeutic strategies has created a new paradigm, and this aspect transforms the cancer treatment field by taking advantage of the immune system of the patient to find and kill tumor cells. Such therapies are immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) T-cell therapies and bispecific T-cell engagers (BiTEs) (2). Although these modalities have shown striking clinical efficacy, particularly in hematological malignancies and some solid tumors, their efficacy mechanism also exposes patients to a group of immune-related adverse events (irAEs), some of which are related to the nervous system and have a different clinical management dynamic. Compared to conventional cytotoxic therapies, immunotherapy-induced anti-tumor effects occur through modulation of the immune system, stimulation of T-cell activity, or a re-direction of immune cells toward tumor antigens which possibly cause off-target immune-mediated destruction of normal tissues. Such immune dysregulation is especially dangerous to the nervous system because of its rich immune milieu and slow regeneration ability. A wide range of diseases in the central nervous system (CNS), peripheral nerves, neuromuscular junction and autonomic nervous systems form a part of neurological irAEs that are specifically induced by cancer immunotherapy. These complications may take the form of mild sensory ones, cognitive problems, or develop into life-threatening conditions such as severe encephalitis, seizures, neuromuscular respiratory failure, Guillain-Barre -syndrome (GBS), and myasthenia-graves like effects (1,2). Neurological irAEs have variable timing, either incurring early in the start of immunotherapy or insidiously weeks to months after the initial treatment has started. It is an unpredictable disease aided by the fact that clinical manifestations tend to be heterogeneous, which makes it harder to diagnose and is most likely not identified early enough. Besides, neurological irAEs may present a differential diagnosis problem because they may overlap with cancer progression symptoms, paraneoplastic syndromes, infections, or other non-infectious adverse effects. The complexity makes it co-requisite to work closely together between oncologists and neurologists among other experts to come up with proper diagnosis and affective management. The pathophysiology of the neurotoxicity caused by cancer immunotherapy continues to be studied. The existing data indicate that such side effects are associated with abnormalities of the autoimmune and inflammatory events induced by immune blockade checkpoint blockade or immune cell therapies. Once activated against cancer cells, there is a possibility

of immune system attacking the neural antigens either by the mechanism of molecular mimicry or by the loss-of-self-tolerance leading to neuroinflammation and tissue destruction (2). Disruption of the blood-brain barrier and penetration of neural tissue by the autoreactive lymphocytes are some of the causes of the clinical manifestations. Nevertheless, the absence of stability biomarkers and thorough knowledge of these immune responses restrain us to forecast who is at danger, and how to personalize prophylaxis. Although neurological toxicities are not as common as other irAEs, they are notably clinically relevant because of their ability to be severe and persist in affecting an individual in the longer term. They can in some instances result in permanent neurological deficit, disability or even death. Early diagnosis and care are necessary because this is vital in preventing irreparable harm. The existing management plans usually entail termination or withdrawal of immunotherapy and starting immunosuppression especially with high-dose corticosteroids. In persistent or high manifestations, more immunomodulatory drugs (such as intravenous immunoglobulin (IVIG) plasma exchange treatment, or various immunosuppressants) may be needed (3). Overall implications of neurotoxicity control and maintenance of the antitumor effect represent a continuing therapeutic contradiction. The increased use of immunotherapy in a wider pool of cancers also indicates that healthcare providers need to be more aware of these neurological problems. Educating on the early indications and symptoms of neurological irAEs is imperative so that intervention occurs accordingly. Moreover, such development will foster multidisciplinary approaches incorporating both oncological and neurological knowledge to assess the patients, stratify the risks, and plan the individual treatment. This review summarizes the recent research studies and clinical evidence of neurologic complications of modern cancer immunotherapy (4). It examines the epidemiology, manifestation and clinical presentation, the underlying immunological mechanisms, diagnostic glitches and the current management paradigms. This work demonstrates more clearly the many complexities involved in neuro-immune interactions in cancer treatment because understanding of this is needed in order to optimize patient care as well as in future studies needed to be researched. Developing new knowledge in the cause and incidence of these adverse events is potentially beneficial to not only advance safety and quality of life among patients but also to improve therapeutic potential of immunotherapy by predicting and curbing toxicities (4). Overall, with the dawn of immunotherapy and its evolving role in transforming the delivery of cancer care, the complication of cancer associated with neurological effects has become an acute area of attention in terms of being vigilant, taking research to understand more how to improve care and collaborate together. These neurotoxicity of the immune system constitute the unique clinical entity that overlaps with both the fields of oncology and neurology creating a steep challenge to clinicians to control the strength of antitumor treatment and preserve neural functioning. Such concerns will need to be faced through constant research, innovation, and a holistic clinical approach that will play a key role in unlocking the full potential of the immunogenic therapy of cancer and ensuring the safety of the patient (1,3).

Methodology

The aim of this study was to conduct a narrative literature review regarding neurological effects of cancer immunotherapy. The procedure involved accepted practices in narrative reviews in terms of the search, screening, and synthesis strategy that was undertaken in the study.

Search Strategy Literature

An extensive literature search was conducted on electronic databases including PubMed/ Google scholar and Web of Science including publications between January 2010 and May 2025. The keywords used in the search strategy and Medical Subject Headings (MeSH) were cancer immunotherapy, immune checkpoint inhibitors, CAR-T cell therapy, bispecific T-cell engagers, neurological complications, neurological toxicity, and immune-related adverse events (irAEs). Results were narrowed using Boolean.

Eligibility Criteria

Studies were considered to be included in case they satisfied following criteria:

Type of study: clinical trials, observational, systematic reviews, meta-analyses, and important case series documenting the neurologic adverse effects of cancer immune therapy.

Population: adult or pediatric patient with immune checkpoint inhibitors (ICIs), a CAR-T cell therapy, or BiTEs.

Outcomes: articles describing incidence, clinical manifestation, diagnostic imaging, pathophysiology or treatment of neurologic immune-related adverse events.

Exclusion criteria were preclinical studies, editorial studies without data and papers that were not related to neurological toxicity.

Selection of research and data extraction

The titles and abstracts were used to screen and determine potentially eligible studies. All the relevant articles were reviewed fully. Manual search for reference lists of the selected papers was also conducted in order to identify other sources. The resulting selection comprised landmark studies and more recent publications in order to give a comprehensive picture.

Main data retrieved were:

Form of immunotherapy (ICI, CAR-T, BiTE), Incidence and time of neuro complications, Spectrum of clinical manifestation (CNS, PNS, a neuromuscular junction, autonomic), Immunological mechanism and pathophysiology proposed, Scales of grading and measurements of diagnosis, Treatment and management quality.

Data Synthesis

Combined results were discussed qualitatively and were divided into subsections, such as epidemiology and incidence, clinical presentation, pathophysiology, diagnostic difficulties, management approaches, and prognosis. There was specific focus on defining areas of agreement, ignorance, and priorities of research in the future.

Discussion:

The discovery and rapid implementation of cancer immunotherapy have completely revolutionized the management of cancer with the possibility of new hope to patients with earlier treatment-resistant and progressive malignancy. Although the efficiency of these treatments can hardly be overestimated, the incidence of adverse events, which fall within the broad range of immune-related effects (irAEs), also includes a complex and mutually influential category of neurological complications (6). This discussion entails a comprehensive review of the neurological toxicities of contemporary cancer immunotherapeutic agents, that is, Immune Checkpoint Inhibitors (ICIs), Chimeric Antigen Receptor (CAR) T-cell therapies, and Bispecific T-cell Engagers (BiTEs) and addresses the issue in terms of incidence, timing, clinical manifestations, pathophysiological issues, diagnostic measures, treatment measures, multidisciplinary care, and prognostic factors (5).

Major Immunotherapy Modalities and Their Neurotoxicity Profiles

Of the multifaceted immunotherapeutic arsenals, ICIs are one of the pillars of multiple solid and hematological malignancies. These monoclonal antibodies bind on the fuel breaks (the immature blockades) of the immune system, mainly CTLA-4, PD-1, and PD-L1, an immune-diversion route that is used by the tumor to avoid being tracked by the immune system (7). ICIs can disinhibit these antitumor tasks by disrupting the inactivation signal of T-cells. Drastic success of e.g. ipilimumab (against CTLA-4), nivolumab, pembrolizumab, cemiplimab (against PD-1), as well as atezolizumab, durvalumab, and avelumab (against PD-L1), has led to FDA approval of more than 60 indications out of 2011. Nevertheless, such activation of the immune system is inevitably connected with improper self-tolerance that results in immune-related adverse events, with neurological immune-related adverse events (irAE-Ns) making a considerable share of them (6). The frequency of irAE-Ns also is determined by the type of ICIs and treatment. The CTLA-4 inhibitors have been associated with neurotoxicity in approximately 38 of the patients, PD-1 inhibitors approximately 61, whereas its combination therapy increases the risks to about 12. Most of these complications relate to the peripheral nervous system (PNS), twice as likely to present as CNS involvement, and shows that ICI is followed by a tendency to cause neuroinflammation or autoimmunity in peripheral nerves (5,6).

A genetically engineered cell-based therapy, CAR T-cell therapy, has brought with it new curative possibilities, especially to B-cell malignancies. By re-tasking the T-cell to vise tumor antigens without the need to interact with MHC antigens, CAR T-cell products including tisagenlecleucel (CD19-directed) idecabtagene vicleucel (BCMA-directed) and other products aimed at CD22 in acute lymphoblastic leukemia provoke strong cytotoxicity against cancerous cells (7). However, these interventions are complexed by immune effector cell-associated neurotoxicity syndrome (ICANS)

which is a neuroinflammatory syndrome potentially life-threatening (8). In the range of 60 to 70 percent, ICANS incidence is strongly related to the severity of the concurrent cytokine release syndrome (CRS), which is another form of systemic inflammatory condition often preceding or accompanying neurotoxicity (8). Notably, ICANS typically occurs within 1-17 days of CAR T-cell therapy, but delayed or recurrent neurological sequelae months later also have been reported. Another group of immune redirecting agents characterized by neurological adverse effects is bispecific T-cell engager antibodies such as blinatumomab that synergistically bind CD3 of T-cells and CD19 of tumor cells. These agents stimulate immune system cells of the affected patient to destroy cancerous cells, although they also may result in neurotoxicity, which is characterized by encephalopathy, seizures and neuromuscular junction (NMJ) disorder (9).

Incidence, Timing, and Patterns of Neurological Complications

The irAEs are presented by the ICIs in up to 12 percent of the patients, and the clinical manifestations target the PNS, mostly, yet CNS are also severely implemented. Neurological symptoms tend to develop early in the course of treatment, but can present at any time, including weeks to months following the end of therapy-any new neurologic manifestation within one year of exposure to an ICI should be whether it qualifies as an irAE-N should be considered as such. The nature of variations in incidence and time of occurrence of specific ICIs implies the need of clinical vigilance during the prolonged patient follow-up (10).

ICANS Incidence attributed to CAR T-cell therapies has been highly inconsistent yet very high in comparison to ICIs. Critical disorders in CRS have a high impact as a risk of ICANS and show overlap and inflammatory continuity of systemic and neurotoxicity. Neurological symptoms tend to appear shortly after infusion, but there have been isolated incidents of permanent or recurrent neurotoxicity six months after the infusion (10). One of the central risk factors that are not always taken into consideration is hyponatremia, that usually precedes ICANS and has to be actively monitored and corrected to prevent neurological aggravation. All in all, the involvement in the peripheral nerve system comprises approximately 75-83 percent of all the neurological irAEs, which is significant evidence of its dominance. In complement, autonomic nervous system (ANS) effects have diverse manifestations such as orthostatic intolerance, cardiac arrhythmias, bowel or bladder dysfunction, which largely are masked by single entity presentations but have a tremendous negative effect on functional status and quality of life (8,10).

Clinical Manifestations: Spectrum of Neurological Symptoms and Syndromes

-Central Nervous System Involvement

The most disabling and worst CNS complications include encephalitis and encephalopathy. The reported prevalence of seizures altered consciousness, psychiatric features, cognitive dysfunction, and movement disorders among approximately 30 percent of patients with neurological irAEs has been reported. The neuro pathology presents itself in diffuse meningoencephalitis or focal localized encephalitis of a particular area of the brain. (11). Immune checkpoint blockade can also cause or

worsen CNS demyelinating an ailment. This entails known multiple sclerosis (MS) relapses or the de-novo. Additional demyelinating disease processes consist of ON, NMOSD, ADEM, and TM. Clinical manifestation of these diseases is highly dependent on the localization of the lesion and includes loss of vision, paralysis, sensory disorders and bladder incompetence (12). Another complication associated with CNS is hypophysis which is inflammation of the pituitary gland whose location is considered as part of the CNS. Among its manifestations, headaches, visual disturbances related to the effect of mass, and hormone insufficiencies (e.g., adrenal insufficiency, hypothyroidism) may be recorded, which may add neurological symptomatology (11).The complexity of clinical issues is also added to scenes by vasculitis syndromes, which include both primary angiitis of the CNS and secondary vasculitis due to systemic autoimmune processes. These vascular inflammations can either involve small or large vessels which include small vessels and large cerebral arteries, which results to stroke-like presentations or progressive neurological deterioration (11,12).

-Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Uniquely to CAR T-cell therapy or BiTE therapy, the terminology ICANS (a constellation of neurologic adverse events) includes a combination of the following neuro-related difficulties: encephalopathy, language dysfunction (aphasia), seizures, cerebral edema, and coma. Cerebral edema is not common but when it does it is fatal. The syndrome arises in most cases after CRS and supports the dual pathophysiology of co-morbidity between systemic inflammatory activation and CNS vulnerabilities (10).

-Peripheral Nervous System and Neuromuscular Junction Disorders

ICI induced neurotoxicity is dominated by peripheral neuropathies. Patients have sensory and motor symptoms including numbness, tingling, and pain; weakness; fractional or gastrointestinal dysmotility; and orthostatic hypotension. Neuromuscular junction diseases comprise immune-mediated ataxia or myasthenia gravis (MG) and myopathies that are characterized by ptosis, diplopia, weakness and fatigability of the muscle. These syndromes can cause acute respiratory syndromes leading to acute respiratory failure that would require acute ventilation (13). Such neuromuscular involvement should have clinical vigilance since they are highly morbid and mortal in case, they remain untreated.

Pathophysiology and Immune Mediators

The mechanism of neurological irAEs is immune dysregulation. ICIs prevent the inhibitory receptors, remove immune checkpoints that impose self-tolerance hence enabling the autoreactive T-cells to damage neural structures. The treatment with CAR T-cells causes widespread cytokine-release, and IL-6 is one of the causative factors of CRS and neurotoxicity. The IFN-gamma mediates substantial impacts on immune responses in CNS, most of which is modeled by the activated CAR T-cells. Interestingly, anti-inflammatory cytokine IL-10 also could promote the production of IFN-gamma, contributing to the development of neuroinflammation. The BBB (blood-brain barrier) integrity tends to break, allowing infiltration of immune cells and cytokines into the CNS parenchyma, therefore promoting

neuronal and glial damage. Production of autoantibodies against neural proteins, molecular mimicry, epitome spreading are suggested possibilities still to be clarified (6,8).

-Diagnostic Considerations and Severity Grading

Neurological irAEs have complex clinical heterogeneity which requires methodical and systematic examination. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 provides a uniform system of neurotoxicity grading, in which it ranges between mild (Grades 1-2) and severe (Grades 3-4). Grade 3 and 4 neurotoxicity include serious cognitive disturbances, encephalitis, global aphasia, myasthenia gravis, myopathies, meningitis or flares of MS also often leading to interruption of immunotherapy (14). A work-up will include neuroimaging to evaluate the demyelination or inflammation or involvement of vasculature. The choice of investigations used in focal CNS lesions is brain and spinal MRI as the modality of first choice whereas in suspected MG cases, Chest CT or chest MRI of the mediastinum assists in ruling out thymoma. Non-specific indicators of systemic inflammation tests run in the lab may include complete blood count (CBC), basic metabolic panel (BMP), liver function tests (LFTs), thyroid stimulating hormone (TSH), ammonia along with blood gases, erythrocyte solarization rate (ESR) and C-reactive protein (CRP) (9,14).

In encephalitic presentations, cerebrospinal fluid is needed especially to exclude the presence of infection as well as ascertain inflammatory markers or autoantibodies. Aquaporin-4 antibodies are also useful in conducting tests on demyelinating disorders like NMOSD. Electroneuromyography helps in the diagnosis of peripheral neuropathy and the disorder of neuromuscular junction (14).

Therapeutic Approaches and Management

Aggressive cases are usually followed by withdrawal of immunotherapy (usually immediately) before initiating immunosuppressants. The mainstay of management is corticosteroids, intravenous methylprednisolone that is preferred in acute severe neuroinflammatory syndromes, particularly ICANS. Dexamethasone is equally popular because it penetrates CNS in addition to promoting the integrity of the blood-brain barrier that prevents neuroinflammatory damage. When refractory, or relapsing symptoms are present, other immunosuppressive therapies including intravenous immunoglobulin (IVIG), and plasma exchange may be implemented. Symptomatic treatment: MG is often treated with pyridostigmine, levetiracetam for antiepileptics or ventilators will be necessary in the case of respiratory failure, neuromuscular failure (12,14).

It is vital to employ metabolic supportive interventions. Hyponatremia correction prior to ICANS development and thiamine supplementation of patients with CRS or severe neurotoxicity have been shown to be of clinical benefit. Neuropathic symptoms are treated using pain agents such as gabapentin and pregabalin whereas hormone replacement is used when there is a failure of endocrine due to hypophysitis. Severe cases and Grade 3-4 events and hospitalization are required along with close control of how fast the person is neurologically deteriorating, early recognition of seizures, and respiratory support (13).

Symptomatic management is equally vital (12):

- Antiepileptic drugs (levetiracetam) for seizures.

- Pyridostigmine and respiratory support in myasthenia gravis.

- Thiamine supplementation to correct deficiency states noted in severe CRS/ICANS.

- Gabapentin or pregabalin for neuropathic pain.

- Hormone replacement therapies in hypophysitis.

Multidisciplinary Collaboration

The best care team to treat neurological irAEs is a multidisciplinary team. The central group of diagnosing and decision making is comprised of oncologists and neurologists. In resistant or difficult patients, consultation of rheumatologists, radiologists, pulmonologists, cardiologists, and ophthalmologists is frequently necessary as irAEs are multi-organ complications, and the complications may arise. There is a special management problem in patients with pre-existing neurological autoimmune disorders who develop duct blockage, MG or multiple sclerosis. Immunotherapy has the potential of worsening these complications, and therefore the treatment option should weigh between the potential positive results on cancer and the risk of affecting the nervous system. It is recommended to use shared decision-making and close monitoring with specific immunomodulatory treatment (14).

Outcomes, Recovery, and Risk Factors

The neurological irAEs range in terms of outcomes, such as full resolution, persistent neurological disability, and death. Female gender and older age have been proved to be demographic risk factors with unfavourable prognosis. An underlying diagnosis of lung cancer with paraneoplastic-like syndromes and circulating neuronal autoantibodies and the initial severity has been associated with a worsened prognosis with regard to neurological recovery (15). Shortened clinical follow-ups are also associated with negative outcomes and hence the worthiness to monitor patients' long term to pick up late or chronic neurological sequelae. Although significant numbers of patients recover fully once immunosuppression is instituted in time, a sizeable proportion is left with lifelong neurological deficits, which demonstrates the permanent consequence of immune-mediated neuroaxonal damage in some patients (13,15).

Key predictors of poor prognosis include (15):

- Advanced age and female sex.

- Presence of paraneoplastic-like antibody syndromes.

- Underlying lung cancer diagnosis.

- High severity at symptom onset.

- Limited duration of follow-up post-irAE onset.

Long-term surveillance is essential to detect delayed complications and manage chronic symptoms, promoting better functional and quality-of-life outcomes (15).

Future Directions and Research Priorities

Nevertheless, larger information gaps still exist regarding pathogenesis, biomarkers, and the best treatment algorithms in terms of recognizing and managing neurological irAEs (16,17). To study neuroimmune crosstalk, immunogenetics and longitudinal follow up patients are vital areas which need to be conducted further. As this paper has demonstrated, the neurological complications of cancer immunotherapy are becoming more complex and require multidisciplinary expertise and close monitoring in addition to multidisciplinary research into improving outcomes among patients (16, 18).

Conclusion:

When it comes to considering the development of the new cancer immunotherapies, including immune checkpoint inhibitors (ICIs) as well as chimeric antigen receptor (CAR) T-cell immunotherapies. Such treatments have had phenomenal progress in oncology across the globe. Our review has reviewed studies in the United States, Belgium, Italy, France, Canada, China and Poland. This presents a broader perspective of the targeted question and enables us to comprehend the neurological issues in cancer immunization in general. Such advances have brought undesirable neuroimmune complications of toxicities along the way including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Corticosteroids and IL-6 inhibitors are some of the strategies that have been used in managing such complications but with lack of adequate evidence and standardization protocols. Although there have been some advances in the way CRS works, the pathogenesis of ICANS and other neurotoxicity can also be studied. The necessity to understand the mechanisms of these toxicities, including the detection of the reliable prognostic biomarkers and the evidence-based recommendations about treatment, requires the initiation of multicentric studies immediately. More recent work on immune-modulatory targets in genetically predictive studies, IL-1 and Gm-CSF, indicate safer immunotherapies are leading to greater insights and rational drug development. Multidisciplinary work between oncologists, neurologists, and immunologists, among others, must be achieved to provide early prognosis, treatment, and the growing satisfaction of patients.

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References:

1-Cuzzubbo S, Javeri F, Tissier M, Colosimo C, Belin C, Ursu R, et al. Neurological adverse events associated with immune checkpoint inhibitors: review of the literature. J Immunother Cancer. 2021;9(7):e002890. doi:10.1136/jitc-2021-002890.

2- Garcia CR, Jayswal R, Adams V, Anthony LB. Neurologic immune-related adverse events associated with immune checkpoint inhibitors: a review of the literature. Front Immunol. 2022;13:829451. doi:10.3389/fimmu.2022.829451.

3-Heinzerling L, Ott PA, Hodi FS, Husain AN, Tajmir-Riahi A, Tawbi H, et al. Management of immune checkpoint inhibitor-related neurotoxicity: consensus recommendations. J Immunother Cancer. 2023;11(8):e006500. doi:10.1136/jitc-2022-006500.

4-Touat M, Lambotte O, Taillia C, Ammari S, Calvo F. Mechanisms and clinical management of immune checkpoint inhibitor–related neurotoxicity. Int J Mol Sci. 2022;23(10):5515. doi:10.3390/ijms23105515.

5-Chen S, Xu Y, Yang Y, Zhou Y, Deng Y, Jiang W, et al. Immune checkpoint inhibitor–associated autoimmune encephalitis: a systematic review. J Exp Clin Cancer Res. 2021;40(1):191. doi:10.1186/s13046-021-02148-6.

6-Guidon AC, Burton LB, Barnett C, Moss R, Giobbie-Hurder A, Oaknin A, et al. Consensus disease definitions for neurologic immune-related adverse events of immune checkpoint inhibitors. Front Neurol. 2021;12:642800. doi:10.3389/fneur.2021.642800.

7-Williams TJ, Benavides DR, Patrice KA, Dalmau J, de Ávila AL, Le DT, et al. Association of autoimmune encephalitis with immune checkpoint inhibitors. Neurology. 2020;95(6):e761–71. doi:10.1212/WNL.0000000000010632.

8-Rubin DB, Danish HH, Ali AB, Li K, LaRose S, Monk AD, et al. Neurological toxicities of chimeric antigen receptor T-cell therapy: pathophysiology and risk factors. Blood. 2023;141(17):2103–15. doi:10.1182/blood.2022017604.

9-Banerjee A, Smith M, Behera P, Rath GK. Neurological adverse events of immunotherapy in oncology: an overview. Curr Oncol. 2023;30(6):440. doi:10.3390/curroncol30060440.

10-Pilotto S, Addeo A, Ferrara R, Bria E, Camerini A, Ciardiello F, et al. Neurologic immune-related adverse events associated with immune checkpoint inhibitors: a multicenter real-world study. Neurol Sci. 2023;44(1):73–82. doi:10.1007/s10072-022-06297-0.

11-Iorio R, Damato V, Evoli A, Carrone F, Palmieri G, Bartoloni A, et al. Clinical features and outcomes of neurological immune-related adverse events induced by immune checkpoint inhibitors. Neurology. 2023;101(2):e161–73. doi:10.1212/WNL.0000000000207592.

12-Strik C, van Kasteren C, van Heerden J, Minnema MC, van de Donk NWCJ, van der Waart AB, et al. CAR T-cell–related neurotoxicity: monitoring and management. J Clin Oncol. 2024;42(15):1689–1701. doi:10.1200/JCO.23.00341.

13-Rogiers A, Postow MA, Zubiri L, Rusman H, Zhu S, Sosa A, et al. Neurological complications of immune checkpoint inhibitors: case series and review. Front Oncol. 2022;12:949142. doi:10.3389/fonc.2022.949142.

14-Ursu R, Belin C, Cuzzubbo S, Carpentier AF. CAR T-cell-associated neurotoxicity: a comprehensive review. Rev Neurol (Paris). 2024 Nov;180(9):989–94. doi:10.1016/j.neurol.2024.07.005.

15-Zamvil SS, Hauser SL, Bar-Or A, Cree BAC, Cross AH, Hartung HP, et al. Immune checkpoint blockade and central nervous system autoimmunity. Ann Neurol. 2023;94(6):993–1006. doi:10.1002/ana.26840.

16-17-Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al.

18-Gust J, Taraseviciute A, Turtle CJ. Neurotoxicity is associated with CD19-targeted CAR-T cell therapies. CNS Drugs. 2018;32(10):1091–101. doi:10.1007/s40263-018-0582-9.

18-Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Neurological toxicity of immune checkpoint inhibitors: real-world experience and review of the literature. Cancers (Basel). 2021;13(9):2064. doi:10.3390/cancers13092064.