IMMUNE CHECKPOINT INHIBITORS AND NEUROTOXICITY: A FOCUS ON DIAGNOSIS AND MANAGEMENT FOR A MULTIDISCIPLINARY APPROACH

Desirèe Speranza[1,], Mariacarmela Santarpia[1,*], Francesco Luppino[2,*], Fausto Omero[1], Enrica Maiorana[1], Mariacarmela Cavalleri[1], Elena Sapuppo[1], Vincenzo Cianci[3], Alessia Pugliese[2], Vito Racanelli[4], Giulia Maria Camerino[5], Carmelo Rodolico[2,°] and Nicola Silvetsris[2,°,§]*

1. Medical Oncology Unit, Department of Human Pathology "G. Barresi", University of Messina, Messina
2. Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
3. Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina
4. Centre for Medical Sciences, CISMed, Department of Internal Medicine Santa Chiara Hospital, University of Trento Trento Italy
5. Department of Pharmacy-Drug Sciences, University of Bari "Aldo Moro", Via Orabona 4, 70125 Bari, Italy

*Co-first name
° Co-last name
§ Corresponding author

Correspondence:
Nicola Silvestris
Medical Oncology Unit, Department of Human Pathology "G. Barresi", University of Messina, Messina
Mail: nicola.silvestris@unime.it

Abstract: Immune checkpoint inhibitors (ICIs) revolutionized cancer treatment by targeting molecules like CTLA-4 and PD-1/PD-L1, utilized by tumors to suppress the immune response. These inhibitors restore T-cell activity, boosting the body's ability to fight cancer. However, the increased activation of the immune system by ICIs can be associated with unique side effects, termed immune-related adverse events (irAEs). Neurological irAEs (n-irAEs) are rare adverse events, affecting around 3.8% of patients receiving anti-CTLA-4 agents, 6.1% of patients receiving anti-PD-1/PD-L1, and 12% of patients receiving combination therapies. Most n-irAEs are low-grade events, while

severe toxicities have been rarely reported. The precise pathophysiology underlying these irAEs is not completely known; suspected mechanisms are cross-reactivity, type IV (T-cell dependent) and type II (IgG dependent) immune mechanisms. The diagnostic algorithm, in accordance with the current guidelines, involves neurological, laboratory and instrumental examinations. Neurological-irAEs therapy includes watchful waiting, discontinuation of ICIs and corticosteroids. Neurological immune-related adverse event (n-irAEs) toxicity may also be an emergent predictive response-related-factor. Patient who experienced n-irAEs showed improved overall survival (OS) and progression-free survival (PFS). A multidisciplinary collaboration, mainly including oncologists and neurologists, is necessary to improve the clinical management of patients experiencing these peculiar immune-related toxicities.

Keywords: immune checkpoints inhibitors, immunorelated adverse events (irAEs), immunotherapy, multidisciplinarity, neurotoxicity.

1. INTRODUCTION

Immune system plays an important role in modulating tumor growth. The inflammatory response, through the activation of different pathways, can both facilitate the tumor growth and determine its arrest through the immune activation. In fact, cancer cells and immune system often coexist in a dynamic equilibrium: the complex interaction between each other can determine the course of the disease and the different response to therapy. Tumor cells must acquire the ability to evade the immune system in order to proliferate and metastasize. Many inhibitory signal transduction pathways maintain immunological tolerance and cellular homeostasis, and they are collectively referred to as immune checkpoints; their main roles are to protect tissues from damage that can occur when the immune system responds to pathogens and to avoid autoimmunity. This is achieved through decreased T-cell activation[1,2].

The use of immune checkpoint inhibitors (ICIs) has markedly changed the treatment and improved the prognosis of various cancer types. These anti-cancer treatments can target negative regulators of the immune response by increasing T-cell activity against tumor cells and blocking the mechanisms exploited by the tumor to suppress the immune response[3,4.]

PD-1 is a cell surface protein expressed by numerous immune cells. Binding between PD-1 and its ligands, PD-L1 and PD-L2, causes immune cell suppression resulting in

peripheral tolerance that facilitates tumor growth. CTLA-4 is a protein receptor that operates as an immune checkpoint and downregulates immune responses[5]. The activation of the above-mentioned pathways inhibits the physiological antitumor activity by T cells and causes peripheral tolerance which facilitates tumor growth[6]. Several monoclonal antibodies targeting immune checkpoints (PD-L1: atezolizumab, durvalumab, and avelumab; PD-1: pembrolizumab, nivolumab, and cemiplimab; CTLA-4: ipilimumab) have been approved by regulatory agencies for an increasing number of oncological indications.

However, the overactivation of the immune system can also lead to a reduced self-tolerance against normal tissues, and this can be correlated to the development of immune-related adverse events (irAEs). Indeed, data from meta-analysis show that 66% of patients receiving immunotherapy develop at least one adverse event of any grade, 14% develop at least one adverse event of grade 3 or higher and the incidence of treatment-related deaths, mainly due to respiratory or cardiovascular failure, is 0.45%. The most common all-grade irAEs are fatigue, pruritus and diarrhoea[7].

Although ICIs toxicities may potentially affect all organs, they involve more frequently the endocrine, the gastrointestinal systems and the skin. Immunotherapy-induced neurotoxicity is rare, affecting 3.8% of patients receiving anti-CTLA-4 agents, 6.1% of patients receiving anti-PD-1/PD-L1, and 12% of patients receiving combination therapies. The low frequency may be correlated to underreported diagnoses. Most of these irAEs are mild or moderate and a small number (0.4-0.7%) of patients experience severe toxicity[8,9].

Neurological irAEs should be promptly recognized and treated correctly, in order to avoid more serious complications, including mortality, and permanent discontinuation of effective treatments. However, this can be challenging in clinical practice because some presenting symptoms of irAEs mimic other more common cancer-related symptoms, or symptoms related to preexisting comorbidities, like fatigue or weakness[10]. So, the assessment of each single case with neurologists is mandatory and can have a significant impact on the diagnosis and proper therapeutic management of these events.

The aim of this review is to analyze the latest data and to provide a practical approach to the multidisciplinary management of cancer patients treated with ICIs and affected by immune-related neurological toxicity.

2. MECHANISM OF ACTION OF IMMUNE CHECKPOINT

The immune system, through the recognition of self and non-self antigens, plays a key role in the elimination of pathogens and abnormal cells, including cancer cells. There are two types of immunity: innate or natural immunity and adaptive or specific immunity. The former is mediated by pre-existing molecules and cells in the body, does not increase in the presence of the pathogen and is non-specific; instead, the latter is induced by the pathogen and activated upon its entry into the body, it mediates the immunological response[11].

There are numerous immune mechanisms capable of inducing the elimination of tumor cells: the immunological surveillance based mainly on the action of cytotoxic T-lymphocytes secreting interferon-γ (IFN-γ) plays a fundamental role[12,13].

In the adaptive immune process, dendritic cells, acting as antigen-presenting cells (APCs), bind antigens to the major histocompatibility complex (MHC) by presenting them to CD8+ and CD4+ lymphocytes.

The immune response utilizes several inhibitory pathways of the immune system to maintain tolerance (preventing autoimmunity) and homeostasis. The molecules involved in these pathways are referred to as immune checkpoints, including PD-1/PD-L1 and CTLA-4; these play a primary role in protecting tissues from cytotoxic damage through T-cell activation and inactivation. Tumor cells can exploit immune checkpoints to evade the immune system and thus avoid immune-mediated destruction[14].

CTLA-4 is expressed on activated T-cells and its primary function is to down-regulate the extent of T-lymphocyte activation. ICIs bind to CTLA-4 and block its immunosuppressive signal leading to T-cell activation, resulting in cytokine and antibody production in the tumor microenvironment[11].

Sometimes, this mechanism can result in unexpected immune-related adverse events due to an autoimmune reaction to normal T-cells[13].

On the other hand, PD-1 is a trans-membrane inhibitory receptor that regulates and maintains the balance between T-cell activation and immune tolerance. Unlike CTLA-4, however, PD-1 is widely expressed and can be found not only on the surface of T-cells but also on the surface of B-cells and NK-cells[12].

While CTLA-4 mainly regulates T-cell activation in lymphatic tissues, PD-1 main role is to limit T-cell activity in peripheral tissues during a cell-mediated or inflammatory immune response[14].

The role and mechanism of action of the immune pathways is shown in Figure 1.

3. NEUROLOGICAL IMMUNO-RELATED ADVERS EVENTS

Neurological irAEs (n-irAEs) are rare events, affecting around 3.8% of patients receiving anti-CTLA-4 agents, 6.1% of patients receiving anti-PD-1/PD-L1, and 12% of patients receiving combination therapies, and they are more frequently of low-grade severity[8,9]. Indeed, around 7.7-11.9 % of all reported irAEs are related to neurological ones. Encephalitis/myelitis, meningitis, peripheral neuropathy (including Guillain-Barré Syndrome; GBS), myasthenia gravis (MG), and myositis are predominantly reported in the Vigibase database (the World Health Organization pharmacovigilance database). Patients with n-irAEs are mainly men, aged 60-70 years and developing toxicity within the first three months after immunotherapy initiation, with most events occurring within the first month[15].

N-irAEs can be divided in central nervous system (CNS) and peripheral nervous system (PNS) events. The most common CNS adverse events are encephalitis, myelitis and meningitis with a total incidence of around 0.46% of patients treated with ICIs[12]. Other rare and later toxicities are: multiple sclerosis (MS), posterior reversible encephalopathy syndrome, neurosarcoidosis[15] , cerebral vasculitis, Tolosa-Hunt syndrome[15] and Vogt-Koyanagi-Harada syndrome[16].

ICI-related peripheral neuropathies have in some cases a high grade of severity > 3 (0.4%). These neuropathies have often an acute or subacute onset and are concomitant with other AEs (58% of cases)[17].

The main reported toxicities are: Guillain-Barré syndrome, polyradiculopathy, chronic inflammatory demyelinating polyneuropathy, polyneuropathy, mononeuritis, cranial polyneuropathy, neuromyopathy and autonomic neuropathy[18].

The exact pathophysiology of irAEs is not completely known. The different possible mechanisms are summarized in figure 2. Immune checkpoints play an important role in downregulating the immune response and modulating its intensity. Although removal of self-tolerance appears to be the trigger for immunotherapy toxicities, its occurrence appears to develop stochastically. Other potential mechanisms may involve shared antigens between the affected tissue and the tumor, leading to cross-reactivity between tumor neo-antigens and normal tissue antigens, but also a direct binding of ICIs to targets expressed in normal tissue (e.g. deposition of antibodies in the pituitary as a consequence of CTLA-4 expression at this level), that can induce toxicity-dependent and complement-mediated inflammation. The reactions which seems to be involved are type IV (T-cell dependent) and type II (IgG dependent) immune mechanisms[19].

Considering the current approved ICIs target PD-1, PD-L1 and CTLA-4, monoclonal antibodies (Abs) against these molecules suppress immunoinhibitory signals on T cells, enabling T-cell proliferation, tumor recognition, and destruction. As part of the immune system, there are regulatory T cells (Treg) that play a key role in maintaining immune tolerance by actively suppressing effector T cells. Tregs also express CTLA-4 and PD-1,

so they are direct targets of ICIs. The loss of immune regulation, added to failure of T-cell tolerance and activation of immune effector cells, might lead to the development of irAEs. ICIs are not tissue specific, so their action isn't limited to the tumor microenvironment. PD-1 and CTLA-4 are expressed in numerous cells and are present in different tissue microenvironments. RNA expressions of PD-1, PD-2, and CTLA-4 have been verified on the entire central nervous system, so it is suggested that these nonhematopoietic cells may be direct targets of ICIs. Molecular mimicry seems to be one of the main mechanisms underlying N-irAEs. For example, there are some shared epitopes between myelin and melanocytes as both originate from the neural crest, and a common mutation in melanoma is related to the normal N -methyl- d -aspartic acid receptor (NMDA). The former mimic is associated with peripheral nerve disease and the latter with encephalitis. Another suggested mechanism for the development of irAEs seems to be epitope spreading. Consequentially to immunotherapy, the release of tumor and nontumor antigens subsequent to tissue damage could facilitate new immune responses that could trigger autoimmunity against normal autoimmune tissues, leading to the development of irAE[20].

4. N-irAEs CLINICAL PRESENTATION

Neurologic adverse events are relatively rare and have different clinical manifestations such as fatigue, headache, dizziness, paresthesias and various clinical syndromes such as myasthenia gravis (MG), Guillain-Barré syndrome (GBS), aseptic meningitis, encephalitis, transverse myelitis, etc. The onset time of neurological adverse reactions varies from several days to several months, with an average onset time of 45 days. As commented before, most of them are mild, nonspecific symptoms. The incidence of severe neurotoxicity is only less than 1%[21]. N-irAEs affecting the peripheral nervous system (PNS-irAEs) are three times more common compared with those affecting the central nervous system (CNS-irAEs) and appear with a shorter latency. ICI-induced neuromuscular events could manifest as neuropathies, involving both cranial and peripheral nerves, neuromuscular junction disorders, or myopathies[22]. A meta-analysis by Xu et al.[16] reported an incidence of grade 3-5 adverse events in the central nervous system (encephalitis, encephalopathy, aseptic meningitis, or myelitis) of 0.46% (22 cases out of 4775 patients exposed to ICIs in 12 studies). In the same study, it was also reported a 5% incidence of peripheral neuropathy of any degree (220 cases out of 4390 patients exposed to ICI in 17 studies), significantly lower than that observed during conventional chemotherapy. Ir-neuropathies are mostly demyelinating and may present as acute polyradiculoneuritis

(Guillain-Barré syndrome, irGBS) with an incidence of about 0.2%-0.4%. Chronic demyelinating neuropathy is less common and appears randomly in elderly women, presenting with paresthesias and weakness. Usually, irGBS can occur early or even several months after initiation of therapy (median of 3-3.5 administered doses of ICI). Similarly to GBS, symptoms of irGBS include symmetric proximal weakness, and involvement of sensory, autonomic and cranial nerves. In cases where only the ventral roots are affected, symptoms may be limited to (asymmetrical) weakness alone. The nerve roots swelling hinders the cerebrospinal fluid flow, causing cytoalbuminologic dissociation and the involvement of cervical nerve roots can induce respiratory failure[19].

Immune-related axonal sensory-motor neuropathies and even pure sensory neuropathies are also described. In general, immuno-related axonal neuropathies tend to be benign and may present as painful, long-term, persistent burning due to small fiber damage, requiring membrane stabilizers such as pregabalin, amitriptyline, or duloxetine[22]. Treatment with ICIs may lead to potential autoimmune disorders. At present, it is believed that ipilimumab may induce T cells to produce antibodies against the acetylcholine receptor, leading to the onset or worsening of myasthenia gravis. With an incidence of <1%, irMG is an increasingly diagnosed AE during ICI therapy. It may, however, be underestimated due to milder cases with nonspecific symptoms such as generalized weakness and fatigue[23]. The incidence of MG was 0.12% in a large group of patients treated with ipilimumab[24]. Clinical manifestations include ptosis, diplopia, muscle weakness, dyspnea, and dysphagia. Rapid disease progression, including bulbar and respiratory symptoms requiring respiratory support, was observed in 50% of patients. In a retrospective cohort of 65 patients with MG (including 20% with preexisting MG), 45% of patients developed respiratory failure. Myasthenic symptoms developed after a median of 4 weeks (1-16 weeks) from the start of ICI; the median time from symptom onset to respiratory failure requiring intubation was only 7 days[25]. MG undergoing ICI treatment is a condition marked by high severity and mortality, significantly higher than the idiopathic forms of MG. In a systematic review by Johansen et al., of 23 cases classified as MG, a 48% mortality rate was reported[25]. In a case series of 12 patients with MG undergoing nivolumab published by Suzuki et al., respiratory support was required in 42% of cases versus 7% in a comparative case series of non-ICI-related MG; the mortality of ICI-related MG reported in the Suzuki et al. study was 2/12 patients (1 for myasthenic crisis, 1 for myocarditis)[26]. From the VigiBase analysis, Johnson et al. identified 233 reported cases of MG, with a mortality of 19.3% (44/228), significantly higher than the other neurological toxicities (11.5% of 444 cases; p=0.024). The mortality was even higher considering cases with association between MG and myositis (20.7%), MG and myocarditis (33%) or both (62.5%), than cases with MG alone

(16.2%)[27]. Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disease characterized by a neuromuscular junction disorder with typical clinical manifestations of proximal muscle weakness, decreased tendon reflexes, and autonomic dysfunction. It is also known as representative paraneoplastic neurologic syndrome (PNS) generally related to small cell lung cancer (SCLC). It is caused by antibodies targeting voltage-gated calcium channels (VGCCs) in the presynaptic nerve terminal. Autoimmunization by the tumor causes LEMS because the same VGCCs are expressed in SCLC[28]. Recently, the addition of anti-programmed cell death-ligand 1 (PD-L1) antibody to chemotherapy in the first-line treatment of SCLC with extensive disease (ED) resulted in significantly longer overall survival than chemotherapy alone. Atezolizumab is an anti-PD-L1 antibody approved for the treatment of ED-SCL. Immune checkpoint inhibitors (ICIs), such as anti-PD-L1 antibody, are known to cause a wide spectrum of immune-related neurological adverse events (n-irAEs), including also LEMS. Several cases of LEMS in patients undergoing immunotherapy, mainly with nivolumab, ipilimumab, and atezolizumab, are reported in the literature[29]. It is also known that the use of ICIs can worsen a preexisting paraneoplastic LEMS. However, considering the severity of the underlying neoplasm, it is not always possible to stop ICI treatment permanently. In these cases, intravenous immunoglobulin therapy is a useful treatment option to control a worsening of paraneoplastic symptoms associated with ICI[30]. Among the myopathies, the most common are autoimmune necrotizing myositis, dermatomyositis, and polymyositis31. Common symptoms include muscle pain, proximal weakness, dysphagia, dysphonia. Since the myocardium and diaphragm could be involved, a prompt diagnosis of IR-myositis is crucial to avoid cardiac or respiratory complications, including long-term disability or mortality. Laboratory tests often show elevated creatine kinase levels. Electrophysiological examination shows myogenic damage. Necrotic muscle fibers and inflammation are observed in skeletal muscle biopsy[32]. Large doses of corticosteroids and discontinuation of ICIs usually improve symptoms, and most patients recover completely. Among CNS-irAEs the most common are immune-mediated encephalitis and aseptic meningitis. About 0.2% of patients treated with PD-1 developed immune-mediated encephalitis, including marginal lobe encephalitis, brainstem encephalitis, and necrotizing encephalitis[33]. The clinical manifestations of immune-mediated encephalitis are not specific, but the main symptoms are headache, fever, mental disturbances, memory impairment, drowsiness, hallucinations, convulsions, neck stiffness, decline in mental status, attention disturbances, and disorientation[34]. Aseptic meningitis is a rare side effect that manifests with nuchal rigidity, headache, and occasionally fever. In contrast to encephalitis, mental status cannot be altered. Cerebrospinal fluid usually shows lymphocytic infiltration and diagnostic magnetic resonance imaging can demonstrate

meningeal enhancement. Other potentially immune-related demyelinating diseases include multiple sclerosis, transverse myelitis, acute-disseminated encephalomyelitis, optic neuritis, and neuromyelitis optica.
It is crucial to acknowledge that patients with neurological toxicity have a longer overall survival.
Spain et al., in a monocentric study of patients with advanced melanoma treated with ICIs, managed at the Royal Marsden Hospital between September 2010 and December 2015, showed better OS 45.7 months (IQR 45.7-45.7m) versus 11.2 months (IQR 4.8-36.6 m), in patients who have experienced neurological toxicity[35,36].

5. DIAGNOSTIC WORK-UP: CLINICAL AND INSTRUMENTAL EXAMINATIONS USED IN CLINICAL PRACTICE

Regarding the diagnosis of N-irAEs, after a review of recent guidelines[37,38,39], it is possible, for the various manifestations, to construct a diagnostic algorithm. Firstly, in case of suspected neurological toxicity, early referral to a neurologist is highly recommended. Patients who develop **encephalitis** require several investigations including: neurological evaluation, rachycentesis for cerebrospinal fluid analysis including cell count, gram stain, bacterial cultures, viral polymerase chain reaction (PCR) for neurotropic viruses, cytologic examination, protein iso-electrofocusing and anti-SNC antibodies (panel for paraneoplastic syndromes and autoimmune encephalitis). Among the instrumental examinations, a MRI and electroencephalogram (EEG) should be performed. Other necessary assessments include hematochemical examinations including metabolic screening (liver and kidney function, ammoniemia, blood glucose), complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), thyroid function and anti-thyroid antibodies (anti-thyreoperoxidase and anti-thyroglobulin). Moreover, other tests that should be considered include antineutrophil cytoplasmic antibodies (ANCA) search (in the presence of suspected vasculitic process), and peripheral smear (to rule out thrombotic thrombocytopenic purpura).
Regarding spinal cord involvement (myelitis), the guidelines recommend: neurological evaluation, diagnostic rachycentesis, MRI of the spine (whole or targeted single segment based on clinical suspicion) and brain with contrast medium, hematochemical tests including vitamin B12 assay, screening for human immunodeficiency virus (HIV) and Treponema pallidum, thyroid function, ANA (anti-nuclear antibody), anti-SNC

antibodies, and monitoring of bowels and urinary disorders to identify possible retentive pictures.

The diagnostic algorithm for Guillan Barré syndrome, on the other hand, involves neurological assessment, diagnostic rachycentesis, MRI of lumbar spinal roots with contrast. It is also recommended to search for antiganglioside antibodies to rule out disease variants (e.g., GQ1b for Miller Fisher). Finally, neurophysiological examination with nerve conduction study is advised.

For neuropathies are required, for a general screening, neurologic evaluation and searching for causes of reversible polyneuropathy such as diabetes, thyroid dysfunction, vitamin B12 and folate deficiency, HIV infection, plasmcellular dyscrasias, systemic autoimmune disorders. For forms with moderate impairment (grade 2) other than a neurophysiologic examination with nerve conduction study, MRI of spinal cord or encephalic MRI, in case of cranial nerve involvement, should be considered and for severe forms (grade 3-4) algorithm for Guillain-Barré syndrome should be applied (Fig.3).

As with neuropathies, the guidelines in myositis also consider the severity of the pathology. In any form of myositis, preliminary evaluation requires neurologic and rheumatologic history, rheumatological (e.g. skin inspection to identify signs suggestive of dermatomyositis) and neurological (with muscle strength examination) physical examination, hematochemical examinations (CPK, AST, ALT, LDH, aldolase), inflammation markers (ESR, C-reactive protein). Anti-acetylcholine receptor antibodies (AChR, to identify possible concomitant MG) or antibodies for neurological syndromes and paraneoplastic myositis can be useful[40]. Other investigations include: neurophysiologic examination, with needle electromyography and neuromuscular junction study to identify possible concomitant MG, nerve conduction study to identify possible concomitant neuropathy, muscle MRI and biopsy in the presence of uncertain diagnosis. The CPK, ESR and C-reactive protein tests are used for follow-up. In neuromuscular junction diseases (such as myasthenia gravis), guidelines include search for anti-AChR-and anti-striatal muscle antibodies on blood (strAb). If negative, it could be considered searching for anti-muscle-specific kinase (MuSK) and lipoprotein-related 4 (LRP4) antibodies. The work-up could also include: blood tests of CPK, aldolase, ESR, C-reactive protein (to identify possible concomitant myositis) and cardiac enzymes (to identify possible concomitant myocarditis). Neurophysiological examination, including neuromuscular junction study (repetitive nerve stimulation test and/or single fiber EMG), nerve conduction study (to identify possible concomitant neuropathy) and needle electromyographic examination (EMG, to identify possible concomitant myositis) is recommended[41]. Pulmonary function study and in the presence of respiratory failure or elevation of CPK and/or cardiac enzymes, cardiologic evaluation

with ECG and transthoracic echocardiogram (to identify possible concomitant myocarditis) should be considered, as well as encephalic and/or spinal cord MRI to rule out alternative diagnoses. N-irAEs diagnostic algorithm is shown in Figure 3.

6. N-IRAES THERAPEUTIC MANAGEMENT

Immune-related neurological complications have never been the subject of specific studies regarding how to define the best pharmaceutical approach that should be used to treat them, however there are some expert opinion and flowcharts based on retrospective case studies.

ESMO[42] guidelines indicates "watchful waiting" as the best approach for grade 1 neurologic irAE, so ICI treatment can be continued, and the patient must be monitored for deterioration. On the other hand, AIOM[37] guidelines suggest the need to consider a possible suspension of ICI treatment in patients with grade 1 neurological toxicity[43], which is actually highly recommended for grade > 1[44]. Data provided by the available literature shows a trend of prioritizing the use of therapeutic schemes currently used in not ICI - related cases. So, it is suggested the oral use of steroids at low dose for mild manifestation or intravenous (IV) steroid therapy at high doses for more serious cases[10].

It should be noted that, unlike canonical cases of GBS, the ICI-mediated development of a GBS-like syndrome was successfully managed using corticosteroid therapy.

Eventually, if the therapy doesn't show any effect, it is suggested the use of intravenous immunoglobulin (IVIG) treatment or plasmapheresis (AIOM) and additional lines of immunosuppressive therapy (NCCN).

According to the available literature and experts' experience, in the presence of grade 1 encephalitis, discontinuation of ICIs and their subsequent re-administration must be discussed with the patient, in the light of risks and benefits[21]. According to ASCO guidelines[39], patients with grade 2 encephalitis require the intake of methylprednisolone 1-2 mg/kg per day[45]; in case of grade 3, in presence of severe or progressing symptoms or oligoclonal bands, must be considered pulse corticosteroids (methylprednisolone 1 g IV daily for 3-5 days) plus IVIG 2 g/kg over 5 days (0.4 g/kg per day) or plasmapheresis[39,46]; while in NCCN guideline[38], therapy includes IV methylprednisolone 1 g daily for 5 days followed by oral tapering (starting with prednisone 1.5 mg/kg per day) over 4-6 weeks after acute phase[47]. In the presence of autoimmune encephalopathy or positivity to paraneoplastic antibodies or if improvement is limited or absent, rituximab should be considered after evaluation with the specialist[38,39]. NCCN guideline includes IV acyclovir until negative PCR results are

obtained[38]; the use of antivirals is also considered a good option in AIOM panels, despite the lack of studies on its efficacy[37]. (Tab. 2)

Due to potential severity of irMG, which can soon lead to respiratory complication, according to ASCO, hospitalization may be appropriate for all grades of severity[39]. In AIOM guideline, beyond traditional therapies, first-line therapy for patients with grade 2 MG should include IV 6-methylprednisolone 1 g/day for 5 days, followed by oral tapering (starting with prednisone 1,5 mg/kg/day)[37,48]. In case of non-responsive patients proceeding with the plasmapheresis or IVIG (0,4 g/kg/day for 5 days) should also be considered[49]. Moreover, it is possible to consider the use of acetylcholinesterase inhibitors (pyridostigmine 60 mg four times a day), which is already recommended by NCCN in grade 2 with dosage of 30 mg TID (ter in die) which has to be gradually increased, in association with a low-dose oral prednisone of 20 mg daily[38]. (Tab. 3)

ASCO suggestions for grade 1 GBS is to continue ICI and monitor symptoms for a week[39]. If symptoms persist, it is crucial to monitor very closely any symptom progression[24]. For grade 2 it is suggested to suspend ICI until the symptomatology returns to grade 1, but also to start oral administration of prednisone 0.5-1mg/kg/day, whereas for G3 a permanent discontinuation of immunotherapy and administration of intravenous methylprednisolone 2-4 mg/kg/day is suggested, and treatment should proceed in the same way as the management of GBS not related to immunotherapy[35]. On the other hand, in case of grade 2 or more GBS, NCCN[38] suggests a permanent suspension of ICI and hospitalization because of the rapidity of respiratory involvement[26,50].

For the management of neuropathic pain, ASCO[39] advises the use of gabapentin, pregabalin or duloxetine, while the NCCN[38] does not recommend the use of opioids[26].

For AIOM guidelines[37], patients affected by GBS related to ICI should be treated with IV methylprednisolone 1 g/day for 5 days, followed by tapering (starting with prednisone 1,5 mg/kg a day)[25,51].

Patients with ICI-related Guillain-Barré syndrome not responsive to corticosteroids should be treated with plasmapheresis or IVIG (0,4 g/kg/day for 5 days)[17]. (Tab. 4)

Myositis is considered a neurological side effect related to ICI[52]. Patients with G1-2 myositis should be treated with oral prednisone 0.5-1 mg/kg/day, followed by tapering. Patients with G3-4 toxicity should be treated with methylprednisolone IV. 1 g/day for 5 days, followed by tapering (starting with prednisone 1.5 mg/kg/day)[53]. Patients who do not respond to corticosteroid therapy should be treated with plasmapheresis or IVIG (0.4 g/kg/day for 5 days)[39,54].

In case of aseptic meningitis, discontinuation of immunotherapy is not needed if mild/moderate, whereas permanently discontinued if severe[55]. Once bacterial and viral infection are excluded, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg/day or IV methylprednisolone 1 mg/kg/day if moderate or severe symptoms[38,39].
Steroids can be tapered after 2-4 weeks, monitoring for symptom recurrence and considering hospitalization for G3-4 toxicity[39].
Grade 1 peripheral neuropathy needs to be monitored for a week without ICI discontinuation[56]. If symptoms are still present, it is important to monitor very closely any kind of progression. NCCN suggest also to suspend immunotherapy[39]. Grade 2 toxicity requires suspension of ICI and observation or intake of prednisone 0,5-1 mg/kg/day (if it progresses from the mild); in case of G3-4, immunotherapy should be discontinued permanently, patients should also be admitted and it is important to request a neurological assessment and start methylprednisolone intravenously 2-4 mg/kg/day[42,57].

ICI-related grade 1 demyelinating diseases including multiple sclerosis (MS), transverse myelitis (TM), acute diffuse encephalomyelitis (ADEM), optic neuritis (ON) and optic neuromyelitis (NMO), do not require therapeutic intervention and allow to continue immunotherapy unless the symptoms worsen. In the case of G2, immunotherapy must be stopped, and patients can start prednisone 1mg/kg per day and reduce for 1 month. Grade 3 and 4 cases will permanently discontinue ICIs; patients must be hospitalized and take methylprednisolone at a dosage of 1g/day and consider IVIG or plasmapheresis if symptoms do not improve or worsen after 3 days[39].
For AIOM guidelines[37], patients with myelitis should be treated with methylprednisolone iv 1 g/day for 5 days, followed by tapering (prednisone 1,5 mg/kg a day), once the infectious investigations are negative[58,59,60].
Other therapeutic approaches such as IVIG and plasmapheresis are not currently recommended, because no good quality evidence is available in the literature even in patients with not ICI-related inflammatory myelopathy[39].

7. CONCLUSION

Neurological irAEs are rare but potentially severe adverse events associated with immunotherapy. Because of severity and the related high mortality, patients suspected to have n-irAEs should be promptly recognized and treated.

For an effective diagnostic work-up and to optimize therapeutic approaches, cancer patients with new neurological symptoms during ICIs should be early referred to neurological consultation. Hence, a close collaboration between neurologists and oncologists is mandatory for the proper management of these patients.

8. EXPERT OPINION

To proliferate and metastasize, tumor cells must be able to evade the immune system and this immunological tolerance is maintained by numerous inhibitory signal transduction pathways, collectively referred to immune checkpoints whose physiological roles are to protect tissues from damage that can occur when the immune system responds to pathogens and to avoid autoimmunity. The tumor's main way of escaping immunologically is by inhibiting T cells. In the last decade, immuno-oncology has transformed the natural history of many cancers and is now a new therapeutic weapon. A reduction in self-tolerance against normal tissues can be correlated with the development of immune-related adverse events (irAEs) due to the immune system's overactivation: at least one adverse event of any grade is developed by 66% of patients receiving immunotherapy. Most frequently irAEs are referred to the endocrine system, the gastrointestinal system and the skin, while neurological toxicity is much rarer. In order to prevent more serious complications, mortality and permanent discontinuation of treatments, it is important to recognize and treat neurological irAEs promptly. A multidisciplinary approach appears necessary in the management of the oncological patient during immunotherapy; in fact, some symptoms of presentation of irAEs mimic other more common symptoms related to cancer or symptoms related to pre-existing comorbidities and this can lead to misdiagnosis. Neurologist plays a crucial role in managing the neurological toxicity of immunotherapic agents in this context and the knowledge of drug-mediated toxicity is enhanced through close collaboration between oncologists and neurologists. In addition, neurologists should be part of the team in the development of guidelines on the management of immunotoxicity, encouraging the neurological point of view and emphasizing the importance of specialistic procedures. Based on current guidelines, it is recommended to assess neurological function, both central and peripheral, in all patients before the start of immunotherapy, with regular reassessment during treatment. It is also important in the event of the onset of neurological symptoms, suspected to be due to immunotherapy toxicity, to proceed, in accordance with the guidelines, with the performance of hematochemical examinations, chemical-physical and infectious analysis of the cerebrospinal fluid and MRI with contrast medium.

Discontinuing treatment with ICIs is not recommended for mild grade, whereas moderate grade toxicity requires temporary discontinuation of the drug with possible subsequent resumption and administration of low-dose corticosteroids. In contrast, high-dose corticosteroid use is recommended for severe n-irAEs (grades 3-4), with the possibility of inclusion of PE or IVIG in cases that do not respond to high-dose steroid therapy. Immunosuppressive agents should be administrated in case of life-threatening. Rechallenge, after discontinuation, of immunological therapy is, on the other hand, not advisable in cases of severe toxicity. In the event of clinical stabilization, tapering of CS within 4-8 weeks is recommended (Figure 4).
However, temporary or permanent discontinuation of immunotherapy and prescription of steroid or immunosuppressive therapy in general must be subject to careful assessment of the severity of the patient's symptoms; continuation of immunological therapy must therefore consider both the risks and benefits for the patient.
Neurological toxicity could also be a useful factor predicting response to immunotherapy[35,36].

Article highlights box

- The discovery of immune checkpoint inhibitors (ICIs) has revolutionized the model of cancer therapy.
- The use of ICI can also lead to a number of immuno-related adverse events.
- Neurological irAEs (n-irAEs) are rare events.
- N-irAEs can be divided in central nervous system (CNS) and peripheral nervous system (PNS) events.
- Neurologists, in collaboration with oncologists, play a crucial role in managing the neurological toxicity of immunotherapeutic agents.

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Declaration of Interest

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