The neurotoxic effects of immune checkpoint inhibitor therapy for melanoma

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The advent of immune checkpoint inhibitors (ICIs), CTLA-4, PD-1 and PD-L1 inhibitors, have dramatically changed outcomes for patients with melanoma and other malignancies [1–3]. With this new class of antineoplastic agents comes a new range of adverse effects. These immune-related adverse events (irAEs) mediated by T-lymphocytes and other mechanisms including enhanced cytokine levels and antibodies [4] are often unpredictable, in contrast to adverse effects seen commonly with cytotoxic chemotherapy.

Few of the initial Phase III trials evaluating the role of ICIs in the treatment of melanoma specifically reported immune-related neurotoxicity. When reported, the incidence of grade 3/4 neurotoxicity was low (<2%) [5]. Increasingly, immune-mediated neurological irAEs are being recognized and reported. Clinical presentation is varied and, while usually occurs early on in the course of therapy, in some cases neurological irAEs may occur many months after cessation of ICI therapy [6,7]. Importantly, the morbidity and mortality associated with this toxicity is relatively high. In a series of 613 fatal ICI-associated toxic events reported by Wang *et al.*, 11% of these were attributed to neurological irAEs [8].

A review by Cuzzubbo *et al.* of neurological irAEs suggests that their incidence is higher with combination CTLA-4/PD-1 inhibition than for either class of agent when used as monotherapy. Interestingly, for monotherapy regimens, the reported rates of any grade neurotoxicity were higher for PD-1 inhibitors compared with CTLA-4 inhibitors (anti-CTLA-4 3.8%, anti-PD-1 6.1%, combination therapy 13%). Severe (Grade 3 or 4) irAEs were infrequent, but more common with anti-CTLA-4 (0.7%) than anti-PD1 agents (0.4%). The majority of cases presented early with a median time to onset of 6 weeks [9]. These data are supported by other 'real-world' single-center retrospective series of patients treated with anti-CTLA-4 and/or anti-PD1 inhibitors [6] or anti-PD-1 inhibitors alone [10], reporting rates of neurological irAEs of 2.8 and 2.9%, respectively. In the former series, 14% of patients receiving combination therapy had neurological irAEs. In all three series, the clinical presentations were varied, highlighting the need for clinical vigilance when assessing patients for suspected irAEs.

Clinical presentations

Neurological irAEs can manifest as a diverse range of symptoms from headache to symptoms and syndromes involving the CNS or peripheral nervous system, the neuromuscular junction or muscle. Presentations can be specific, mimicking known neurological syndromes, or, perhaps more commonly, nonspecific, leading to under-reporting of this toxicity. Nonspecific presentations may include dyspnea secondary to respiratory muscle involvement or constipation secondary to enteric neuropathy, both of which might easily be attributed to other etiologies [11].

One of the most frequently reported presentations involving the CNS is encephalopathy. This encompasses a broad range of underlying conditions including encephalitis, vasculitis, stroke, multiple sclerosis and posterior reversible encephalopathy syndrome [9]. Larkin *et al.* reviewed in detail six reported cases of encephalitis. All patients had altered mentation with a variety of other symptoms including headache, fever, confusion, aphasia,

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agitation, difficulty walking or standing, seizures and fatigue. At least two patients had lymphocytosis (>70%) in the cerebrospinal fluid (CSF). Five of the six patients recovered, all of whom received intravenous corticosteroids [12].

Other reported presentations involving the CNS are: aseptic meningitis (15% of patients with neurological irAES in Cuzzubbo's review of 59 clinical trials [9]) – CSF in such cases often has a lymphocyte predominance and symptoms are generally steroid-responsive [11]; and multiple sclerosis-like syndromes including transverse myelitis and optic neuritis [7,11].

Peripheral neuropathies (sensory and motor) are the most commonly reported neurological irAEs and are generally mild (Grade 1–2) [11]. Peripheral neuropathies encompass a broad range of conditions including mononeuropathy, mononeuritis multiplex, polyneuropathy, meningoradiculitis, chronic inflammatory demyelinating polyneuropathy and acute inflammatory demyelinating polyneuropathy or Guillain-Barré (GB)-like syndromes.

Among a large cohort of 10,277 patients treated with ICIs in Japan, Suzuki *et al.* reported 12 (0.12%) cases of myasthenia gravis (MG). Compared with a control group of patients with idiopathic MG, those with ICI-related MG had a predilection for more a severe and rapidly deteriorating disease course, including respiratory muscle involvement and myasthenic crisis warranting respiratory support [13]. Multiple cases of myositis have also been reported, characterized by an elevated creatine kinase and features of necrosis on biopsy [10,14].

Increasingly, reports are emerging of patients with overlapping neurological irAEs. Several cases of ICI-related myositis and concurrent MG have been reported (42% of cases in the review by Suzuki *et al.*) [13,15]. Additionally, reports are emerging of other life-threatening irAEs coexisting with neurological irAEs such as myocarditis, most notably in the analysis of fatal irAEs by Wang *et al.*, where concurrent myasthenia gravis was noted in 5/52 (10%) of patients with myocarditis [8]. In another series, 40% of patients with myositis had evidence of myocarditis [14].

Response to ICIs

In studies where disease response data have been evaluated, the majority of patients with reported neurological irAEs demonstrated a response to treatment. In the Royal Marsden Hospital series, 70% of patients with a neurological irAE had an objective response and median survival was 45.7 months [6]. This is equivalent to the rate reported by Cuzzubbo *et al.*, where 11/16 (69%) of patients with a neurological irAE had responded [9].

Investigations

Investigating patients with suspected neurological irAEs requires exclusion of differential diagnoses, which may often require urgent treatment to prevent life-threatening complications, such as hypophysitis, malignancy (parenchymal or leptomeningeal disease or paraneoplastic syndromes) infection or stroke [12]. Aside from presenting symptoms, history should also include potential infectious disease exposure and recent vaccinations.

As such, depending on the clinical presentation, investigations may include septic screening, examination of the pituitary-hypothalamic axis, an autoimmune and vasculitis screen, creatine kinase levels, computed tomography, MRI/magnetic resonance angiography, lumbar puncture and examination of CSF, electroencephalogram, electromyography and nerve conduction studies. Where MG is suspected, a tensilon test may be warranted. For both MG and GB-like syndromes, monitoring of vital capacity and maximum inspiratory and expiratory pressures is important due to risk of rapid decompensation requiring ventilatory support. Cardiac evaluation in any case of suspected MG or myositis should be undertaken as well as creatine kinase in MG.

Management

While there is no evidence-based approach, similar to most irAEs, the principles of the initial management of neurological irAEs involve withholding of the ICI for grade >1 toxicities and commencement of corticosteroids [11]. Clinicians should have a low threshold to withhold ICIs for any grade of suspected neurological syndrome and monitor closely given that even mild peripheral neuropathy may develop into an ascending polyneuropathy with respiratory involvement. Where other potentially life-threatening conditions form part of the differential diagnosis, these should also be treated empirically, for instance, viral or bacterial meningitis. Supportive therapy may also be indicated, such as pyridostigmine for MG and/or ventilatory support for MG and GB-like syndromes. Early allied health input is usually warranted, given the potential morbidity of long-term neurological sequelae [6]. For those requiring long-term corticosteroids, prophylactic antibiotics to reduce the risk of opportunistic infection should also be considered.

Increasingly, it is recognized that management paradigms are not always the same as for non-ICI neurological disorders. For instance, there appears to be a role for corticosteroids for ICI-related GB-like syndromes, with cases responding to steroids-alone whereas for idiopathic GB, steroids are generally not indicated [9].

Neurologist input should be sought early in cases of neurological toxicity, especially in steroid-refractory cases as there is no standard second-line treatment. In GB-like syndromes or MG, intravenous immunoglobulin or plasmapheresis may be required. Use of immunomodulators such as mycophenolate mofetil, tacrolimus and infliximab may also be considered in other steroid-refractory cases. Recently, the use of natalizumab was described for management of limbic encephalitis [16]. International guidelines for management of irAEs incorporate an approach to neurological toxicities [17].

Rechallenge

The safety of rechallenging with ICIs after a prior neurological irAE is unknown. Despite cessation of ICI therapy due to toxicity, many have ongoing durable responses [6,9]. For patients with disseminated melanoma, targeted therapy should be used where possible, but options are often limited. In this situation, a very careful risk–benefit analysis is warranted. Cases have been reported of patients receiving subsequent ICIs (± steroid cover) after a neurological irAE without any recurrence of the initial neurological irAE [13,18,19].

Future perspective

Further research is required to understand the mechanisms behind the diverse spectrum of immune-related neurological toxicities. In turn, this will hopefully shed light on the most appropriate way to manage these challenging irAEs. As ICIs are now approved as adjuvant therapy for melanoma in several countries, patients who could be otherwise cured of disease may be at risk of significant treatment-related morbidity. The nonspecific nature of presentations and the relatively infrequent incidence of severe neurological irAEs highlights the importance of clinician awareness of these events. Developing clear communication pathways for patients to report in symptoms of concern enables early recognition. Prompt assessment and management within a multidisciplinary team that involves a neurologist should be prioritized. In future, the development of specialist multidisciplinary meetings for the discussion of irAEs may assist in streamlining management for this complex patient group [20].

Author contributions

L Spain and R Wong contributed to the design, writing and review of this manuscript.

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