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Editorial

Immune checkpoint inhibitors and neuropathy: A new dawn

See Article, pages 1440–1445

Immune checkpoint inhibitors (ICPI) have been successfully utilized in the treatment of a variety of malignancies, becoming first-line treatment for non-small cell lung cancer, metastatic renal carcinoma and BRAF wild-type melanoma, as well as sarcoma, colon and bladder cancer (Groisberg et al., 2017; Hammers et al., 2017; Overman et al., 2017; Weber et al., 2017; Horn et al., 2018; Paz-Ares et al., 2018; Socinski et al., 2018; Cella et al., 2019). Neurological complications have emerged as a potential side-effect of ICPI therapy with an incidence of 2–4% (Dalakas, 2018). Most of these neurological complications (6–12%) are classified as mild, presenting as headaches, dizziness, paresthesias or small-fiber sensory neuropathies, and don't impact ICPI therapy. Serious neurological complications are evident in <1% of ICPI treated patients and include inflammatory myopathies (dermatomyositis, polymyositis and necrotizing autoimmune myositis), myasthenia gravis, aseptic meningitis, autoimmune encephalitis, CNS demyelinating diseases (either *de novo* or exacerbation of pre-existing multiple sclerosis) and hypophysitis (Dalakas, 2018; Psimaras, 2018; Perrinjaquet et al., 2019). These complications may occur between 1 and 12 weeks after commencement of ICPI therapy and are responsive to treatment with steroids, intravenous immunoglobulin, plasmaphereses or immunosuppressant medications (Dalakas, 2018).

Peripheral neuropathies are an extremely rare complication of ICPI therapy, occurring in less than 1% of treated cases. Autoimmune-mediated neuropathies, such as chronic inflammatory demyelinating polyneuropathy, Guillain–Barré syndrome and Miller-Fisher syndrome are the most frequently reported (Liao et al., 2014; Cuzzubbo et al., 2017; Baird-Gunning et al., 2018; Dalakas, 2018). While the mechanisms underlying the development of autoimmune neuropathies with ICPI remains to be fully elucidated, molecular mimicry has been invoked as a possible process.

In this issue of *Clinical Neurophysiology*, Chen and colleagues report on the largest series of ICPI mediated peripheral neuropathy and provide in-depth clinical and neurophysiological phenotyping (Chen et al., 2019). Importantly, immune-mediated demyelinating neuropathies predominated, although axonal sensorimotor polyneuropathy and painful pure sensory axonal neuropathies were also evident along with non-specific myopathies. A variety of ICPIs were used, including anti-PD-1 (nivolumab and pembrolizumab), anti-PD-L1 (atezolizumab) and anti-CTLA4 (ipilimumab) antibodies, suggesting a calls effect. The close temporal association between ICPI therapy and development of neuropathy (median time, 4 weeks), along with a clinical response of the neuropathy to corticosteroids and immunomodulating therapy suggests a causal association.

The pathophysiological mechanisms underlying the development of ICPI mediated neuropathies remains to be fully elucidated. Therapeutic inhibition of checkpoint blockade appear to unleash an autoimmune response directed against compact myelin and antigens located on motor and sensory axons. The factors governing selective vulnerability of the myelin and axon, and thereby mediating specific clinical phenotypes, need to be further addressed. In addition, although neuromuscular complications will remain rare adverse events of ICPI therapy, with greater therapeutic use they are likely to add to the disease burden of cancer patients. A greater understanding of the mechanisms predisposing to development of ICPI-induced neuropathy, as uncovered for chemotherapy induced neuropathies (Park et al., 2008, 2009), could be important in formulating future management strategies in order to avoid the development of debilitating neuropathies, ultimately impacting on survival and life quality in cancer patients.

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Conflict of interest

None.

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