Neurological toxicity induced by immunotherapy

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Cancer immunotherapy has resulted in a paradigm shift in onco-hemathology. Immunotherapy may be active, inducing an immunotherapy response in vivo. This is the case of vaccine or oncolytic virus that directly sensitizes the immune system to tumor-specific antigens. Or it may be passive, by transferring cells or antibodies which have been previously manipulated in vitro, and that will target the tumor or will modulate the natural immune response of the patient. Among immunomodulatory strategies, immune check point inhibitors (ICPi) are antagonistic antibodies that block specific immune checkpoint molecules, aiming to enhance general immunoreactivity by augmenting co-stimulatory molecules or blocking inhibitory molecules. Unfortunately, by unbalancing the immune system, these immunotherapies may however generate dysimmune toxicities.

Neurological immune related adverse events (irNRLAE) induced by ICPi are thought to result due to the loss of maintenance of self-tolerance and a pathological abnormal immunologic activation, which can affect such as the peripheral as the central nervous system (CNS). Different irNRLAE have been described, including encephalitis, myelopathy, aseptic meningitis, meningoradiculitis, Guillain-Barré-like syndrome, peripheral neuropathy (including mononeuropathy, mononeuritis multiplex, and polyneuropathy) as well as myasthenic syndrome, which often vary in severity from mild transient peripheral neuropathies that resolve spontaneously, to persistent conditions that require prolonged treatment. Neuromuscular manifestations are the most common, and frequently overlap syndromes with multiple irNRLAEs or other affected organ systems frequently exist. For example, concomitant myasthenia gravis-myositis-myocarditis represents a life-threatening continuum of neuromuscular and cardiac toxicity.

This presentation focuses specially on one of the CNS toxicities, immune-related encephalitis (irENC) reported with ICPi, which despite being less frequent (0.1–0.2% of patients treated with ICPi), tend to be challenging and serious, sometimes fatal, highlighting the need for its promptly recognition and treatment. Unfortunately, similar to other irNRLAE, only limited information regarding incidence, characteristics, and outcome of associated with irENC is available as most information is derived from isolated case reports or rudimentary safety reports collected in the frame of clinical trials. As a result, the relatively short term collective experience available information is widely variable regarding diagnosis as well as treatment approaches. A systematic literature search, up to December 2018 was conducted in PubMed database to review the reported clinical picture of irENC.

Clinical presentation includes change in alertness and attention, confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality and hallucinations with sudden, transient, or progressive onset, sometimes resembling limbic encephalitis, with variable intensity and frequently associated to fever. Onset of encephalitis can occur early (within a few weeks) or late (7–12 months) after ICPi initiation, and even occur after discontinuation of ICPi therapy. Course is usually monophasic despite relapses have been described. Patients under combination of immunotherapy appeared to suffer more severe and refractory syndromes and earlier presentation.

Importantly, patients under ICPi therapy can develop a number of neurological symptoms that may or may not be directly related to their therapy, and neurologic consultation is mandatory. The symptoms associated with irNRLAEs can range from mild (grade 1-2) to severe (grade 3-4); however, they are often challenging to diagnose like neuromuscular complications that they may present as generalized symptoms, such as fatigue and weakness, that can also be caused by the cancer itself. In the case of irENC, differential diagnosis may rule out metastases, metabolic disorders, stroke, infectious encephalitis and neurological adverse effects of previous therapies such as irradiation. After CT scan, lumbar puncture should always be performed and typically CSF shows lymphocytic pleocytosis (<250/mm3), with elevated protein (usually < 150 mg/dL) and normal glucose. However, normal CSF may not exclude the possibility of irENC and it was strictly normal in 5 cases reported in the literature. MRI of brain ± spine with contrast must be done, and may be unremarkable or show T2 hyperintensities. EEG to evaluate for subclinical seizures is recommended.

The optimal management of neurological irAEs including irENC has not yet been established. Treatment is empirically based on the standard of care for the induced disease, mostly based on expert opinions and the knowledge of autoimmune diseases, rather than prospective studies. In a patient with suspected irENC, ICPi may be withholding immediately. Consider concurrent antiviral (i.e., acyclovir) and/or bacterial therapy until negative PCR results obtained. Prednisolone doses ranging 1 -2 mg/kg or in those severe cases 1 gr x 3 or 5 days, and plasmapheresis, intravenous immunoglobulin (IVIG) or other or immunosuppressive approaches depending on the evolution have been reported to be of benefit. The duration of treatment with immune-suppressive agents has not been tested prospectively but is recommended a full steroid dose treatment course of 2–4 weeks followed by a gradual taper to avoid recurrence. Characteristically, neurological symptoms and signs remit within 48-72 hour following initiation of steroid therapy, and in despite in the majority of reported cases, the neurological outcome of the patients has been favorable, fatal outcome can be possible.

In summary, the time of irNRLAE, and specifically irENC onset is unpredictable, and evolution may be rapid and life-threatening. Although rare, they will likely be encountered with increasing frequency as ICPi therapy expands to other cancers. Early recognition, cessation of immunotherapy, prompt investigation and immunosuppression treatment is crucial for timely improvement of functional outcome and requires a multidisciplinary approach.

Bibliography

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