



Neurological complications of anti-PD-1 antibodies: shall we be more concerned?

Kyrillus S. Shohdy¹, Omar Abdel-Rahman²

¹Clinical Oncology Department, Kasr Alainy School of Medicine, Cairo University, Cairo, Egypt; ²Clinical Oncology Department, Faculty of medicine, Ain Shams University, Cairo, Egypt

Correspondence to: Omar Abdel-Rahman. Clinical Oncology Department, Faculty of medicine, Ain Shams University, Cairo, Egypt.

Email: omar.abdelrhman@med.asu.edu.eg.

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Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target receptors expressed on surface of T-lymphocytes and tumor cells, those receptors such as programmed death receptor-1 (PD-1), and the programmed death-ligand 1 (PD-L1) mediate an immunosuppressive state characterized by T cell anergy that enables institution of tumorigenesis. ICIs boost the effector immune cells to get rid of tumor cells efficiently. A wide-range spectrum of immune-related adverse effects (ir-AEs) was expected to emerge with the increasing use of those agents. Mechanisms of those ir-AEs are not clear, it was thought to be due to production of antibodies from activated B cells or macrophage-mediated toxicity, in addition to the fact that ICIs unleash the self-reactive T cells (1).

Most of the ir-AEs occur at very low incidence in clinical trials with exception of endocrine dysfunctions and gastrointestinal adverse effects (2). Since targeting the first immune checkpoint receptor, CTLA-4, the neurologic adverse effects (nAEs) emerged as a real concern. One meta-analysis of 59 clinical trials (including 9,208 patients), has found that the overall incidence of nAEs reaching 3.8% with anti-CTLA4 antibodies, 6.1% with anti-PD1 antibodies, and 12.0% with the combination of both (3).

Neurologic complications of ICIs constitute heterogeneous constellations of adverse effects that are usually not properly characterized in large meta-analyses of clinical trials. For instance, one meta-analysis of safety of PD-1/PD-L1 inhibitors compared to chemotherapy

has collected data on 12 clinically relevant symptoms. The only reported nAE was sensory neuropathy that was found significantly lower in the PD-1/PD-L1 inhibitor group compared with the chemotherapy group (1.2% versus 8.6%; RR =0.16) (4). Looking into the increasing rate of approvals of ICIs, the real-world clinical data became readily available for further assessment of the safety and efficacy of those drugs. Scrutinizing the evidence on the pattern and severity of neurologic complications with each ICIs and each tumor histology is required due to the associated treatment-related mortality (like the case with pneumonitis) (5).

Kao *et al.*, have published in *JAMA Neurology*, a retrospective cohort study representing one of the largest real-world experience on neurologic complications of anti-PD-1 antibodies (6). The study focused on anti-PD-1 agents (pembrolizumab or nivolumab) to determine the frequency and severity of nAEs. The study was meant to be a real-world experience through including patients received those agents after their approval from US Food and Drug Administration (FDA). The study retrospectively reviewed 347 patients (59% received pembrolizumab and 41% received nivolumab). The treatment-related neurological complications have occurred in ten patients in this cohort. This low frequency of 2.8% was really reassuring. Most of the patients were elderly (median age of 71 years) and has advanced melanoma or lung cancer. Previous history of autoimmune or neurologic disease was evident in none. Seven of those events occurred with

Table 1 Characteristics of the retrospective studies on neurologic complications of immune checkpoint inhibitors

Study	Sample	Type of cancer	Treatment	nAEs, n (%)	Most common AE	Outcome
Kao <i>et al.</i> , 2017 (6)	347	Variable	Anti-PD1	10 (2.9)	Neuropathy [4]; myopathy [2]	Resolved [9]; death [1]
Spain <i>et al.</i> , 2017 (8)	352	Melanoma	Anti-CTLA-4 and/or anti-PD-1	10 (2.8)	Neuropathy [6]; aseptic meningitis [3]	Resolved [8]; ongoing symptoms [2]
Zimmer <i>et al.</i> , 2016 (7)	496	Melanoma	Anti-PD-1	16 (3.2)	Varied neuropathy [9]; seizures [2]	Resolved [10]; not improved (6 including one death)

nAEs, neurologic adverse effects; AE, adverse effect.

pembrolizumab. Neuropathy and myopathy were the most common nAEs. Co-incident ir-AEs occurred in five patients mainly hypothyroidism and colitis. The study did not find any clear pattern of nAEs, the number of treatment cycles to onset of nAEs was variable (range, 1–20 cycles) and the median time from therapy initiation to maximum symptom severity ranged from 1 day to more than 3 months. What is interesting in this study is the detailed description of every neurologic complication, sometimes with confirmation of the diagnosis with electromyography (EMG), magnetic resonance imaging (MRI) and tissue biopsy. The diagnosis of nAE is cumbersome, as the presentation might be non-specific such as, headache, dizziness, asthenia, and lethargy (7). On histopathological examination, the two cases of myopathy showed muscle fiber necrosis and the sural nerve biopsy from one patient with severe subacute asymmetric neuropathy revealed necrotizing vasculitis. Although the authors did not report the grade of nAEs based on common terminology criteria for adverse events (CTCAE), they reported the modified Rankin Scale (mRS) score. This scale ranges from 0 (no symptoms) to 6 (death). In this cohort, the median mRS was 2.5 indicating mild to moderate disability. This score might be of value in assessing nAEs in clinical trial setting instead of the conventional CTCAE. All patients discontinued treatment and received immunosuppressive agents namely, corticosteroids (7 patients), IVIG (3 patients) and plasma exchange (1 patient). Only one patient succumbed to severe necrotizing myopathy. Other severe nAEs such as encephalitis and aseptic meningitis were not seen in this cohort.

Of paramount importance, the authors tried to investigate the pathophysiology of those immune-related events, most of the serum connective tissue markers and autoimmune panels were negative except one patient with necrotizing myopathy who was positive for anti-PM/Scl antibodies (these antibodies are associated with polymyositis and systemic scleroderma overlap syndromes). This patient

died and was refractory to corticosteroids and three sessions of plasmapheresis. Inflammatory findings were evident on imaging and mixed B and T cells infiltrate was seen in biopsy from patients with polyneuropathy.

The results of this study were consistent with a previous retrospective analysis of 496 melanoma patients receiving anti-PD-1 antibodies (see *Table 1*). Of this cohort, 16 nAEs were reported (3.2%), most of them were grade 1–2 and resolved spontaneously or with corticosteroids (7). It is worth noting that several case reports published individually documenting nAEs of ICIs might give false impression of higher incidence and severity of this category of complications. In systemic review of 191 publications (reporting on 251 cases), the incidence of nAEs was 9.6%, however, most cases were with ipilimumab (anti-CTLA-4 antibody). This might be due to including only reports before August 2015 (9).

Another point of debate is the proper algorithm of treatment. In most occasions, corticosteroids are the first choice (10). It is still not clear what should be the next step for steroids-resistant cases. Further research on pathophysiology of these events might help in proper characterization of the sequence of treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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