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Central nervous system toxicities of anti-cancer immune checkpoint blockade

Jonathan T. Blackmon[1], Toni M. Viator[2], Robert M. Conry[3]*

[1]Covenant College, USA
[2]University of Alabama at Birmingham, USA
[3]Division of Hematology Oncology, University of Alabama at Birmingham, USA

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***Correspondence:**
Dr. Robert M. Conry, MD
Melanoma Program Director
Associate Professor, Division of Hematology Oncology, University of Alabama at Birmingham
2145 Bonner Way,Birmingham, AL 35243, USA Telephone: (205) 978-0257
Fax: (205) 978-3928
Email: rconry@uabmc.edu

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ABSTRACT

Immune checkpoint inhibitors (CPIs) which unleash suppressed antitumor immune responses are revolutionizing the systemic treatment of cancer. Durable responses and prolongation of survival come at a price of frequent immune-related adverse events resulting from inflammation of normal tissues. Herein, we review serious central nervous system (CNS) toxicities of immune CPIs including ipilimumab, nivolumab, pembrolizumab and atezolizumab. Case reports of 20 patients with CPI-associated encephalitis, meningitis, or myelitis were reviewed as well as data from large scale registration trials. The overall incidence of serious immune-related CNS toxicities is approximately 0.4-1% with the potential for hundreds of cases annually in the United States. Patients suspected of having serious CPI-associated CNS toxicity should have a neurology consult, lumbar puncture, and MRI of the affected regions. If confirmed, the offending drug should be permanently discontinued and high dose intravenous steroids initiated, preferably with 500-1,000 mg of methylprednisolone daily. With timely diagnosis and appropriate management, the majority of patients experience complete neurologic recovery. As the array of indications for CPIs rapidly increases, it is imperative for clinicians to have a high index of suspicion for immune-related CNS toxicities.

Abbreviations: CPI: checkpoint inhibitor, CNS: central nervous system, CTLA: cytotoxic T-lymphocyte antigen, PD: programmed cell death, PD-L: PD-1 ligand, APCs: antigen presenting cells, MRI: magnetic resonance imaging, PRES: posterior reversible encephalopathy syndrome, CSF: cerebrospinal fluid

Intorduction

Immune checkpoints refer to a variety of inhibitory pathways integral to the immune system that maintain self-tolerance and modulate the duration and magnitude of physiological immune responses to minimize collateral tissue damage. Key checkpoints exploited for anti-cancer therapy include cytotoxic T-lymphocyte antigen (CTLA)-4 and programmed cell death (PD)-1 proteins on the surface of T-cells which respectively bind to B7-1 and B7-2 on antigen presenting cells (APCs) or PD-1 ligands (PD-L1 and PD-L2) on tumor cells or APCs[1-3] Physiologic engagement of CTLA-4 tolerizes effector T-cells and enhances the immunosuppressive effects of regulatory T-cells in the systemic circulation and lymph nodes[4]. In contrast, binding of the PD-1 receptor to its ligands occurs primarily in peripheral tissues such as tumor-infiltrating lymphocytes and promotes T-cell exhaustion that limits cytokine release, proliferation, and cytolytic activity[5]. Ipilimumab, an anti-

CTLA-4 monoclonal antibody, was FDA-approved for first line treatment of advanced melanoma in 2011[6,7]. Pembrolizumab and nivolumab are anti-PD-1 monoclonal antibodies approved by the FDA in 2014 for advanced melanoma and now collectively also indicated for non-small cell lung cancer, renal cell carcinoma and Hodgkin's lymphoma[8-12]. Most recently, atezolizumab, an anti-PD-L1 monoclonal antibody binding to the other side of the PD-1/PD-L1 interaction, was FDA-approved for advanced urothelial carcinoma[13]. These immune CPIs are rapidly revolutionizing the systemic therapy of cancer. The American Society of Clinical Oncology cited immunotherapy as the 2016 clinical cancer advance of the year, and immunotherapy has recently earned its place as one of the five pillars of cancer treatment alongside surgery, radiotherapy, chemotherapy, and targeted therapy[14].

Durable responses and prolongation of survival with immune checkpoint inhibitors come at a price of frequent immune-related toxicities resulting from inflammation of normal tissues. The most frequent grade 3 or 4 serious adverse events include dermatitis, colitis, hepatitis, thyroiditis, hypophysitis, pneumonitis, and nephritis[15]. Collectively, serious adverse events affect approximately 15% of patients receiving anti-PD-1 therapy, 25-40% of those receiving ipilimumab, and 55% of patients receiving combination treatment with ipilimumab and an anti-PD-1 antibody[1-3,6,7]. The higher incidence of immune-related adverse events observed with ipilimumab, which targets CTLA-4, is thought to be a consequence of systemic versus peripheral effects of CTLA-4 and PD-1 inhibition, respectively[4,5]. Serious adverse events are managed by holding the checkpoint inhibitor and initiating high dose steroids, typically 1-2mg/kg of oral prednisone daily to taper gradually over one month[15].

Serious neurological adverse events affect approximately 1% of patients receiving immune checkpoint inhibitors[16,17]. Transient sensory and motor peripheral neuropathies are the most common. Rare cases of autonomic neuropathy, Guillian-Barre syndrome, and myasthenia gravis-type syndrome affecting the peripheral nervous system have also been reported[16,18,19]. Since melanocytes and Schwann cells are derived from neural crest with antigenic similarity, the pathogenesis of immune-related neuropathy often involves autoantibodies against shared ganglioside epitopes[19]. Herein, we review serious CNS toxicities of immune checkpoint inhibitors. Although uncommon, these events pose significant risk for long-term morbidity or mortality if not recognized early and appropriately treated. A systematic review of the English literature using PubMed and Google Scholar completed June 22, 2016 revealed 20 relevant case reports with patient characteristics summarized in Table 1. Immunosuppressive treatment for CNS adverse events and clinical outcomes are provided in Table 2. The great

Patient	Age	Cancer	CPI	CNS Toxicity	Duration of CPI before onset	MRI abnormal	CSF lymphocytosis	Reference
1	41	Melanoma[a]	Ipi[b]	E[c] (splenium)[d]	3 doses (2 mo)[e]	yes -b[f]	yes	16
2	50	Melanoma	Ipi	E (granulomatous)	NS[g] doses (2 mo)	yes -b	yes	15
3	76	Melanoma	Ipi	E (splenium)	4 doses (4 mo)	yes -b	NS	20
4	71	Melanoma-unknown primary	Ipi	E	2 doses (3 mo)	no -b	no	21
5	58	Melanoma-vaginal	Ipi	E (PRES)[h]	1 dose (<1 mo)	yes -b	NS	22
6	64	Prostate	Ipi	E	7 doses (12 mo)	no -b	no	23
7	NS	Pancreatic	Ipi	E	2 doses (1 mo)	no -b	no	24
8	55	Melanoma	Ipi + Nivo[i]	E	1 dose (<1 mo)	no -b	yes	25
9	65	Small Cell Lung	Ipi + Nivo	E (limbic)	1 dose (<1 mo)	yes -b	yes	25
10	26	Hodgkin's Lymphoma	Ipi → Pembro[j]	E (PRES)	5 doses (8 mo)	yes -b	NS	26
11	70	Non-Small Cell Lung	Nivo	E (limbic)	14 doses (NS mo)	yes -b	NS	27
12	64	Melanoma	Pembro	E (limbic)	18 doses (12 mo)	yes -b	yes	28
13	51	Melanoma	Pembro	E (splenium)	36 doses (21 mo)	yes -b	no	29
14	56	Melanoma-ocular	Ipi	Meningitis, E	4 doses (4 mo)	yes -b	yes	30
15	52	Melanoma	Ipi	Meningitis	1 dose (1 mo)	NS	yes	15
16	56	Melanoma	Ipi	Meningitis	4 doses (NS mo)	no -b/yes -s[k]	yes	31
17	51	Melanoma	Ipi	Meningitis	1 dose (<1 mo)	no -b	yes	32
18	NS	Renal Cell	Ipi	Meningitis	4 doses (NS mo)	no -b	yes	33
19	58	Melanoma	Ipi	Myelitis	2 doses (5 mo)	no -b/yes -s	yes	34
20	45	Melanoma	Ipi	Myelitis, E (PRES)	4 doses (3 mo)	yes -b/yes -s	yes	35
				Median	**4 doses (3 mo)**			

[a] Cutaneous melanoma unless otherwise specified; [b] Ipilimumab; [c] Encephalitis; [d] Focal involvement of the splenium of the corpus callosum on brain MRI; [e] Months; [f] Brain MRI ; [g] Not specified; [h] Posterior Reversible Encephalopathy Syndrome; [i] Nivolumab; [j] Pembrolizumab; [k] Spinal MRI

Table 1. Patient Characteristics from Case Reports

Patient	Steroids[a]	Other Immunosupression	Time to Recovery	Neurologic Recovery	Tumor Response
1	180 mg	None	3 mo[b]	Complete	CR
2	HD[c]	None	<1 mo	Complete	ND
3	HD	Cytoxan	2 mo	None	ND
4	1,000 mg	None	<1 mo	Complete	SD
5	NS[d]	None	<1 mo	Complete	PD
6	1,000 mg	None	10 mo	Partial	CR
7	NS	None	NS	Complete	ND
8	1,000 mg	IVIg[e] + Rituximab	4 mo	Complete	PR
9	48 mg	None	1 mo	Complete	PR
10	None	None	<1 mo	Complete	PR
11	112 mg[f]	None	NA	Death	ND
12	HD	None	5+ mo	None	SD
13	1,000 mg	None	2 mo	Partial	ND
14	112 mg[f]	None	3 mo	Complete	ND
15	NS	None	NS	Complete	PD
16	1,000 mg	IVIg	24 mo	Complete	CR
17	43 mg	None	<1 mo	Complete	SD
18	HD	None	<1 mo	Complete	ND
19	HD	IVIg	7+ mo	None	PD
20	56 mg[f]	Infliximab	2+ mo	None	ND
			Median 2 mo		

[a] Daily methylprednisone dose or equivalent; [b] Months; [c] High dose, not otherwise specified; [d] Steroids given but dose not specified; [e] Intravenous Immunoglobulin; [f] Assuming 70 kg body weight

ND: No Data CR: Complete Response PR: Partial Response SD: Stable Disease PD: Progressive Disease

Table 2. Treatment and Clinical Outcomes from Case Reports

majority of case reports included an exhaustive search to exclude infection, tumor progression, or other etiologies for CNS dysfunction, which was attributed in all cases to immune-related adverse events of checkpoint inhibition. Published reports of large scale, registration-enabling trials were also reviewed pertaining to the four FDA-approved checkpoint inhibitors. Warnings and precautions from the full prescribing information for each drug were examined to better estimate the incidence of serious CNS toxicities. Tumor pseudoprogression is another mechanism of CNS deterioration associated with immune checkpoint blockade that is not the subject of this review[36,37]. Pseudoprogression refers to increased mass effect at tumor foci resulting from a desired influx of T-lymphocytes and other inflammatory cells following immune checkpoint blockade.

Summary of case reports

Encephalitis

Thirteen case reports of immune-related pure encephalitis and two additional cases associated with meningitis or myelitis were identified. Ipilimumab monotherapy was responsible for 9 of 15 cases (60%), simultaneous or sequential use of ipilimumab with an anti-PD-1 antibody accounted for another 20%, and the remaining 20% involved anti-PD-1 monotherapy. Clinical onset of pure encephalitis occurred a median of 2.5 months following initiation of CPI with a median of 3.5 doses administered. There was considerable variation in onset of encephalitis ranging from less than 1 month to 21 months after CPI initiation with 1 to 36 doses administered. As with encephalitis from other causes, the most frequent signs and symptoms included headache, fever, confusion, disorientation, memory impairment, somnolence, and gait ataxia. Tremors, seizures, and hallucinations were also frequently reported. Symptom onset was typically acute to subacute over days to a few weeks. One patient apparently had chronic onset with gradual decline of memory and language proficiency over one year preceding the diagnosis of encephalitis[28]. Focal abnormalities were reported on magnetic resonance imaging (MRI) of the brain in 11 of 15 patients (73%) with encephalitis (Table 1). Recurring patterns on brain MRI included involvement of the limbic system, the splenium of the corpus callosum, or posterior reversible encephalopathy (PRES) in three patients each. Biopsy of a splenial lesion in patient 3 revealed acute and subacute inflammatory demyelination (20). Cerebrospinal fluid (CSF) revealed lymphocytic inflammation in five patients (56%) with pure encephalitis and was normal in the remaining four patients examined. Electroencephalograms showed generalized slowing in four of five encephalitis patients examined (80%), two of whom had non-diagnostic brain MRIs[23,25,28,30,35]. Subclinical epileptiform activity was also identified in one patient.

Initial treatment for pure encephalitis consisted of steroids in 12 of 13 patients (92%), and one patient

recovered following discontinuation of CPI without immunosuppressive therapy[26]. Steroid therapy was typically intravenous and referred to as "high dose" in 10 of 12 pure encephalitis patients. The maximum steroid dose was specified in seven cases and consisted of 1,000 mg per day of methylprednisolone in four and 0.5-2 mg/kg per day of methylprednisolone or equivalent in the remaining three. Only one case of pure encephalitis was treated with immunosuppression other than steroids. Anti-N-Methyl-D-aspartate receptor antibodies were documented in the CSF of this patient who showed no clinical improvement with 1,000 mg of daily methylprednisolone or intravenous immunoglobulin but recovered completely following rituximab[25] . Among patients with pure encephalitis, 8 of 13 recovered completely (62%) within a median of less than one month. Two patients partially recovered with significant residual neurologic deficits 2-10 months after onset. Two patients survived without meaningful neurologic recovery over 2-5 months, and an additional patient's death was attributed to immune-related encephalitis[27,28].

Meningitis

Five cases of immune-related meningitis were reported, all following ipilimumab and one associated with encephalitis. Clinical onset of meningitis occurred within one month following 1-4 doses of ipilimumab (median 4 doses). Reported signs and symptoms were diverse but included combinations of fever, severe headache, neck pain or rigidity, photophobia, sensory or motor cranial nerve findings, and gait ataxia. Brain MRI was abnormal in 1 of 4 patients examined, showing meningeal enhancement[30]. Spinal MRI revealed arachnoiditis in the only patient imaged[31]. CSF universally demonstrated lymphocytosis with elevated protein. Patient 14 underwent dural biopsy demonstrating acute and chronic inflammation[30]. Initial treatment for immune-related meningitis consisted of steroids in all five cases, typically by intravenous administration. Steroids were described as "high dose" in 4 of 5 cases ranging from 0.5 mg/kg to 1,000 mg daily of methylprednisolone or equivalent. One patient also received intravenous immunoglobulin[31]. All five meningitis patients recovered completely over periods of 1-24 months (median 2 months).

Myelitis

Two cases of immune-related myelitis were reported, both following ipilimumab and one associated with PRES[34,35]. Clinical onset of myelitis occurred after two to four doses of ipilimumab and three to five months following CPI initiation. Presenting symptoms included paraplegia, urinary retention, constipation, and sensory loss in the lower extremities. Spinal MRI demonstrated diffuse intramedullary edema from the cervical cord through the cauda equina in patient 19 and focal intramedullary lesions in patient 20. CSF showed lymphocytic inflammation in both patients. Biopsy of an enhancing conus lesion in patient 20 showed necrotizing myelopathy with lymphocytic infiltration. Initial therapy consisted of high dose steroids for both patients followed by intravenous immunoglobulin or infliximab. Despite subsequent spinal MRI showing marked regression of intramedullary edema, patient 19 achieved no meaningful neurological recovery over seven months. Encephalopathy resolved two weeks after steroid initiation in patient 20, but no clinically meaningful improvement occurred in myelopathy over two months of treatment.

Discussion

Full prescribing information from the manufacturers of each of the four FDA-approved immune checkpoint inhibitors describe a <1% incidence of immune-related encephalitis with a more specific incidence of 0.2-0.5% calculable from the labels of pembrolizumab and ipilimumab/nivolumab combination therapy. Immune-related meningitis is cited by the labels of ipilimumab and atezolizumab as affecting fewer than 1% of patients with a more specific incidence of 0.4% calculable among patients receiving adjuvant high-dose ipilimumab. A report of patients from the registration trial for adjuvant ipilimumab actually describes lymphocytic meningitis in 7 of 475 patients (1.5%) frequently associated with flu-like symptoms and suggests that pauci-symptomatic meningitis may be under diagnosed in patients with headache that frequently accompanies CPI therapy[31]. Thus, data from over 3,000 cancer patients involved in registration trials of CPIs indicate a combined incidence of serious immune-related CNS toxicities in the range of 0.4-1%. For comparison, the incidence of paraneoplastic syndromes affecting the CNS among cancer patients not receiving immunotherapy is < 0.1%[38]. Furthermore, de novo CNS paraneoplastic syndromes occur predominantly in patients with small cell lung cancer, breast cancer, or ovarian teratoma rather than melanoma as reported here. Statistics from the American Cancer Society indicate approximately 200,000 people die each year from cancers with an FDA-approved indication for CPIs, suggesting the potential for 800 to 2,000 cases annually of immune-related CNS toxicities in this country as CPIs become more widely used.

Ipilimumab as a single agent or in combination with anti-PD-1 antibodies was associated with 85% of immune-related CNS toxicity case reports. This reflects the greater risk of serious immune-related adverse events of all organ systems with ipilimumab: 25% with standard dose monotherapy, 40% with high dose monotherapy, and 55% when combined with anti-PD-1 treatment[1,6,7]. Melanoma involvement in 70% of CNS toxicity case reports likely reflects it being the only FDA-approved indication for ipilimumab. The incidence of CNS adverse events may be

increased by concomitant use of CPIs with chemotherapy or kinase inhibitors as described for immune-related toxicities affecting other tissues[39,40]. Similarly, enhancement of systemic immunity following local radiotherapy for cancer, termed the abscopal effect, may increase the incidence of immune-related adverse events when combined with checkpoint blockade[41].

There is virtually no direct evidence concerning the pathogenesis of CNS toxicities following immune checkpoint blockade. However, clinical observations and murine models of CNS paraneoplastic syndromes provide insight into the mechanisms underlying neuronal inflammation. Paraneoplastic disorders of the CNS can be divided into four groups based upon pathogenesis. (1) The classical paraneoplastic disorders, such as anti-Hu, involve T-cell targeting of CNS neurons with antibodies being a marker of specific immune response but not directly pathogenic[42]. (2) Other syndromes involve antibodies specific for intracellular synaptic proteins including GAD65, amphiphysin, and Nova2 where a transgenic mouse model indicates a combination of cellular and humoral immunity is required to break CNS tolerance[43]. (3) Another group involves antibodies to CNS neuronal membrane proteins such as the N-methyl D-aspartate receptor (NMDAR) where antibodies are themselves pathogenic[44]. (4) Inflammatory demyelinating disorders are associated with T-cell activation in the peripheral blood and elevated serum levels of inflammatory cytokines and are represented by the experimental autoimmune encephalitis mouse model of multiple sclerosis[45]. For example, elevated levels of interleukin-6 and tumor necrosis factor alpha are associated with cancer immunotherapy and neuroinflammation[46,47]. Thus, immune-related CNS toxicities following immune checkpoint blockade likely involve varied mechanisms including neuronal damage by T-cells, autoantibodies and/or cytokine-mediated inflammation with implications for reversibility based upon pathogenesis. In steroid refractory patients, clinicians should consider cytokine suppression with infliximab or tocilizumab, inhibition of antibody production by rituximab, or effector T-cell inhibition by tacrolimus or cyclosporine. Selection from among these therapies may be guided in part by identification of signature autoantibodies.

For patients suspected of having CNS toxicity associated with immune checkpoint blockade, a neurology consult, lumbar puncture, and MRI of affected regions should be considered. EEG may be helpful in the setting of suspected encephalitis with a normal brain MRI or to exclude seizure activity. If a serious immune-related CNS toxicity is confirmed, therapy with the offending CPI should be permanently discontinued. Intravenous methylprednisolone initially at 500-1,000 mg daily for 3-5 days should be strongly considered. If clinical improvement is observed, methylprednisolone can be tapered over several days to 1-1.5 mg/kg daily followed by discharge on oral prednisone at 1 mg/kg daily with the daily dose reduced by 10 mg every four days to wean steroids over 4-6 weeks. Peak concentrations and the area under the curve for free-prednisolone are approximately 4-fold lower in CSF than plasma[48,49]. Thus, the widely used dose of 125 mg daily for colitis, dermatitis, hepatitis, or nephritis may be insufficient to treat CNS inflammation. All five patients with meningitis and 8 of 13 patients with encephalitis recovered completely. The patient with chronic onset of encephalitis achieved no neurological recovery but did stabilize with treatment. Neither patient with myelitis experienced meaningful recovery despite evidence of inflammation responding to immunosuppression. Tumor response to immune checkpoint blockade was evaluable in 12 of 20 case reports following the onset of CNS toxicity. Objective responses occurred in 6 of 12 patients (50%) with 3 complete responses (Table 2). Thus, high dose steroids and other immunosuppressive agents required to manage CNS toxicities apparently did not adversely effect the efficacy of checkpoint blockade, consistent with observations following the treatment of other serious immune-related adverse events[50].These cases indicate the need for earlier diagnosis and intervention before necrosis and irreversible deficits ensue. As CPIs are approved for a rapidly expanding array of indications, it is increasingly important for neurologists, oncologists, and primary care physicians to understand the diagnosis and treatment of immune-related CNS toxicities.

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