Review

Neurological adverse events associated with immune checkpoint inhibitors: Review of the literature

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Abstract Immune checkpoint inhibitors (ICIs) targeting CTLA4 and PD1 constitute a promising class of cancer treatment but are associated with several immune-related disorders. We here review the literature reporting neurological adverse events (nAEs) associated with ICIs. A systematic search of literature, up to February 2016, mentioning nAEs in patients treated with ICIs was conducted. Eligible studies included case reports and prospective trials. One case seen in our ward was also added. Within the 59 clinical trials (totalling 9208 patients) analysed, the overall incidence of nAEs was 3.8% with anti-CTLA4 antibodies, 6.1% with anti-PD1 antibodies, and 12.0% with the combination of both. The clinical spectrum of neurological disorders was highly heterogeneous. Most of these nAEs were grade 1–2 and consisted of non-specific symptoms such as headache (55%). The incidence of high grade nAEs was below 1% for all types of treatment. Headaches, encephalopathies and meningitis were the most commonly reported (21%, 19% and 15%, respectively). Among the 27 case reports, the most common nAEs were encephalopathies, meningoradiculoneuritis, Guillain-Barré like syndromes and myasthenic syndromes. The median time of nAEs onset was 6 weeks. In most cases, drug interruption and steroids led to neurological recovery, even in conditions where steroids are not usually recommended such as Guillain-Barré syndrome.

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1. Introduction

Anti-CTLA4 (ipilimumab, tremelimumab) and anti-PD1 (nivolumab, pembrolizumab, lambrolizumab, pidilizumab) monoclonal antibodies enhance antitumour immunity by targeting T-cells inhibitory receptors. These antibodies, classified as immune checkpoint inhibitors (ICIs), have recently obtained approval for treatment in metastatic melanoma [1–5], non-small cell lung cancer [6–8], renal-cell carcinoma [9] and are currently under clinical trials in several other indications. Immune checkpoint inhibitors have undoubtedly been a major step forward in immunotherapy these last years, having significantly increased survival of cancer patients.

As might be expected, adverse effects (AEs) can occur through immunologic activation, that have been termed immune-related adverse events (irAEs) or, occasionally, adverse events of special interest. Grade 3 and 4 adverse events occurred in 13–55% of ipilimumab-treated patients, in 9–43% of nivolumab-treated patients, in 11–14% of pembrolizumab-treated patients and in 54–86% in ipilimumab plus nivolumab-treated patients [10]. These irAEs can potentially involve every organ system but gastrointestinal, dermatologic, hepatic, endocrine and pulmonary toxicities predominate [11,12]. Although rare, neurological adverse effects (nAEs) require prompt recognition and treatment to avoid substantial morbidity.

This review summarises the published data on neurological toxicities reported with immune checkpoint inhibitors, trying to define their incidence, timing patterns, clinical and paraclinical presentation.

2. Patients and methods

A systematic literature search, up to February 2016, mentioning treatment with immune checkpoint inhibitors on adult human beings and published in English was conducted in PubMed database, using the keywords: ‘ipilimumab or tremelimumab or nivolumab or pembrolizumab or lambrolizumab or pidilizumab or anti-CTLA4 or anti-CTLA-4 or anti-PD1 or anti-PD-1’ and ‘clinical trials’. Observational studies were excluded. For the case reports search, the keywords used were ‘safety or toxicity or sides effects or adverse events’ and ‘anti-CTLA4 or anti-CTLA-4 or anti-PD1 or anti-PD-1 or ipilimumab or tremelimumab or nivolumab or pembrolizumab or lambrolizumab or pidilizumab’. Abstracts in medical meetings were not searched.

To be eligible for our analysis, patients could have received previous oncologic therapies, but those who received anti-CTLA4 or anti-PD1 antibodies in combination with other treatments were not. Cases of typical myositis, uveitis and hearing loss without primary neurological involvement were excluded. Patients with brain metastases or tumoural meningitis were also excluded in case reports but trials with patients with controlled brain metastases were included.

Two investigators performed the reading and data extraction independently. They used, for each article, a standard data extraction form and re-read together the articles in the event of any discrepancy.

The incidence of neurological treatment-related AEs (nAEs) was calculated using the total number of nAEs/number of patients exposed to the drug within prospective clinical trials (phase I, II and III). The AEs grade was recorded according to version 2, 3 or 4 of the Common Terminology Criteria for Adverse Events of the National Cancer Institute, and grade ≥3 were considered high grade.

In case reports, patient characteristics, regimen treatment, the nature of each neurological AE, their onset, the biological and instrumental tests realised, and their outcome were recorded. Neurological AEs were classified according to the nervous system area involved: encephalopathy, myelopathy, pure meningitis, meningo-radiculitis, Guillain-Barré like syndrome, peripheral neuropathy and myasthenic syndrome. Encephalopathy included all types of parenchymal lesion, such as vasculitis, stroke, multiple sclerosis, or posterior reversible encephalopathy syndrome (PRES). Neuropathy included all types of peripheral involvement (mononeuropathy, mononeuritis multiplex and poly-neuropathy), except the cases in which cerebro-spinal fluid (CSF) analysis showed any abnormalities (hyperproteinorachia or pleocytosis). In these cases, the neuropathy was reclassified as a meningo-radiculitis in case of pleocytosis or as a Guillain-Barré like syndrome in case of isolated hyperproteinorachia.

3. Results

3.1. Literature search

The Pubmed search identified 82 relevant publications for the present study: 59 clinical trials (totalling 9208 patients exposed to anti-CTLA4 or anti-PD1 antibodies) and 23 case reports reporting 26 cases. One case seen in our ward was added to the case reports. Among the 59 clinical trials, 37 were investigating anti-CTLA4 antibodies (7 phase I, 24 phase II, 6 phase III), 22 anti-PD1 antibodies (9 phase I, 6 phase II, 7 phase III) and 4 a combination of both (1 phase I, 1 phase II, 2 phase III; Supplementary data, Tables S1, S2 and S3). The main underlying cancers in clinical trials were melanoma (5518 treated patients), non-small-cell lung cancer (1847 treated patients) and renal-cell carcinoma (678 treated patients).

3.2. Incidence of neurological AEs in prospective trials

We first focused on patients included in prospective trials (phase I, II and III), without considering case reports, to
get an unbiased picture of the overall incidence of nAEs. Among the 9208 patients exposed to immune checkpoint inhibitors, the overall incidence of any grade nAEs was 3.8% with anti-CTLA4 antibodies, 6.1% for anti-PD1 antibodies and 12.0% with the combination of them (Table 1). However, most of these nAEs were grade 1–2 and consisted of non-specific symptoms such as headache (55%), dysgeusia (13%) or dizziness (10%; Fig. 1A). The incidence of high grade (Gr 3–4) nAEs was below 1% for all types of treatment (Table 1, Fig. 1B). The spectrum of neurological symptoms appeared to be highly heterogeneous (Fig. 1). No clear association between neurological syndromes and the ICI type (Supplementary data, Tables S4 and S5) was seen.

No clear relationship between the incidence of nAEs and drug dosage was seen in 3 studies comparing different doses of anti-CTLA4 antibodies [13–15]. For patients receiving anti-PD1 antibodies, the incidence of nAEs was higher with nivolumab at 10 mg/kg when compared with lower doses [16–19], but the reverse situation was observed with pembrolizumab [7,20–23].

3.3. Clinical presentation in case reports

We then focused on case reports (27 patients) to better define the spectrum of neurological syndromes related to immune checkpoint inhibitors therapy (Table 2). Median age of cases was 56 years old, with a range from 31 to 81 years, and there was a slight male predominance (18/27). Patients were mainly treated for melanoma (25/27 cases) with ipilimumab (21/27 cases). Overall median time of onset of nAEs was 6 weeks (1–74). The presentation was acute or sub acute in all cases. When tumour evolution was mentioned, nAEs were associated with tumour response in 11/16 patients (69%).

Peripheral nervous involvement was the most frequently described presentation in case reports (n = 13/27), even without considering myasthenic syndromes (n = 5/27). These peripheral involvements encompassed a large spectrum of overlapping diseases, ranging from focal neuropathies, peripheral neuropathies, Guillain-Barré like syndromes and meningoradiculitis. Unfortunately, electrophysiological and CSF studies were not always performed and/or reported (9/13 and 8/13 reported data, respectively), leaving the type of neuropathy (axonal, demyelinating) and precise anatomical involvement unclear. In meningoradiculitis cases, imaging showed typical cranial and/or spinal nerves enhancement in 4/6 cases. In myasthenic syndromes, anti-AChR antibodies were found in all cases, and a myositis was associated in 2 cases [24,25]. Encephalopathies cases were very heterogeneous, including demyelinating diseases with a case of

Table 1
Incidence of neurological AEs in patients included in clinical trials.

<table>
<thead>
<tr>
<th>Class antibody</th>
<th>Drugs</th>
<th>Nber of pts</th>
<th>Incidence of any grade nAEs % (range of reported incidence)</th>
<th>Incidence of grade 3–4 nAEs % (range of reported incidence)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CTLA4</td>
<td>All</td>
<td>3672</td>
<td>3.8 (0–27.3)</td>
<td>0.7 (0–7.1)</td>
<td>[1,2,13–15,53]</td>
</tr>
<tr>
<td></td>
<td>Ipilimumab</td>
<td>2734</td>
<td>3.0 (0–22.2)</td>
<td>0.8 (0–7.1)</td>
<td>[54]</td>
</tr>
<tr>
<td></td>
<td>Tremelimumab</td>
<td>938</td>
<td>6.3 (0–27.3)</td>
<td>0.3 (0–3.5)</td>
<td></td>
</tr>
<tr>
<td>Anti-PD1</td>
<td>All</td>
<td>5076</td>
<td>6.1 (0–26.8)</td>
<td>0.4 (0–5.0)</td>
<td>[5,6,8,16–19,68–75]</td>
</tr>
<tr>
<td></td>
<td>Nivolumab</td>
<td>2536</td>
<td>5.2 (0–23.5)</td>
<td>0.4 (0–5.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>2333</td>
<td>6.3 (0–26.8)</td>
<td>0.2 (0–1.7)</td>
<td>[7,20–23,53,76]</td>
</tr>
<tr>
<td></td>
<td>Lambrolizumab</td>
<td>135</td>
<td>21.5</td>
<td>0</td>
<td>[3]</td>
</tr>
<tr>
<td></td>
<td>Pidilizumab</td>
<td>72</td>
<td>5.6</td>
<td>5.6</td>
<td>[77]</td>
</tr>
<tr>
<td>Anti-CTLA4</td>
<td>All</td>
<td>460</td>
<td>12.0 (10.2–18.9)</td>
<td>0.7 (0–2.1)</td>
<td>[4,78,79]</td>
</tr>
</tbody>
</table>

Bold represents the overall incidence values for anti-CTLA4, anti-PD1 treatments and association of both. Italic represents the incidence values for each specific anti-CTLA4 or anti-PD1 drug.

Fig. 1. Clinical pattern of neurological adverse events associated to ICIs in clinical trials. Other severe nAEs: 1 motor dysfunction [39], 3 pain in extremity [49], 1 hydrocephalus [14], 1 dizziness [47], 1 paraesthesia, 4 not specified nAEs [2,18], 2 intracranial haemorrhages, 1 glioma [77]. Two severe AEs reported respectively as disorientation and gait disorder and confusion were interpreted as encephalopathy [23,71].
Table 2 - Clinical pictures of neurological AEs (nAEs) reported in case reports (n = 27).

<table>
<thead>
<tr>
<th>AEs</th>
<th>Drug</th>
<th>Time to nAE onset (median days)</th>
<th>Abnormal CSF analysis</th>
<th>Treatment</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalitis (n = 6)</td>
<td>Anti-CTLA4: n = 4</td>
<td>6 (10–18)</td>
<td>3/4 (pleocytosis in 2/4)</td>
<td>Drug discontinuation only n = 2</td>
<td>Death n = 4</td>
<td>[26, 28, 30, 32, 80]</td>
</tr>
<tr>
<td>Meningitis (n = 2)</td>
<td>Anti-PD1: n = 3</td>
<td>8 (45–150)</td>
<td>1/10 (pleocytosis in 1/10)</td>
<td>Steroids only n = 3</td>
<td>Partial recovery n = 2</td>
<td>[31, 86]</td>
</tr>
<tr>
<td>Myelitis (n = 2)</td>
<td>Anti-CTLA4: n = 4</td>
<td>36 (7–72)</td>
<td>1/1 (pleocytosis in 1/1)</td>
<td>Steroids + PE/IV Ig n = 3</td>
<td>Partial recovery n = 1</td>
<td>[31, 88]</td>
</tr>
<tr>
<td>Meningoradiculitis (n = 5)</td>
<td>Anti-CTLA4: n = 5</td>
<td>84 (35–91)</td>
<td>3/3 (pleocytosis in 0/3)</td>
<td>Drug discontinuation only n = 1</td>
<td>Death n = 1</td>
<td>[28, 35, 89, 91]</td>
</tr>
<tr>
<td>Guillain-Barre’s syndrome (n = 4)</td>
<td>Anti-PD1: n = 1</td>
<td>28 (12–30)</td>
<td>N/A</td>
<td>NA</td>
<td>Partial recovery n = 4</td>
<td>[29, 30]</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Anti-CTLA4: n = 3</td>
<td>36 (7–72)</td>
<td>N/A</td>
<td>NA</td>
<td>Partial recovery n = 1</td>
<td>[29, 30]</td>
</tr>
<tr>
<td>Myositis (n = 3)</td>
<td>Anti-CTLA4: n = 3</td>
<td>36 (7–72)</td>
<td>N/A</td>
<td>NA</td>
<td>Partial recovery n = 1</td>
<td>[29, 30]</td>
</tr>
<tr>
<td>Sarcoidosis (n = 1)</td>
<td>Anti-CTLA4: n = 1</td>
<td>36 (7–72)</td>
<td>N/A</td>
<td>NA</td>
<td>Partial recovery n = 1</td>
<td>[29, 30]</td>
</tr>
</tbody>
</table>

Taken together with anti-PD1 antibodies (0.4%). Surprisingly, when

exacerbation of multiple sclerosis [26], brain vasculitis [27], and PRES-like syndromes [28].

Outcome of nAEs showed a partial or complete neurological recovery in 73% of cases (20/27), with a median delay of 4 weeks. Five patients died although the relationship with the nAE was unclear in 2/5 cases [29, 30]. Clinical improvement was only reported in patients for whom ICI drug was stopped. Among these patients, 12 patients (44%) received steroids in monotherapy and 8 (30%) steroids in association with intravenous immunoglobulin or plasma exchanges.

### 3.4. Histological analysis

In 6 cases (2 encephalitis, 1 meningitis, 1 meningo-radiculitis, 1 Guillain-Barré like syndrome and 1 peripheral neuropathy), histological analysis was performed [29–34] and consistently showed inflammation with lymphocytic infiltrates supporting an immune-mediated disease. This inflammation was perivascular in 4/6 cases and involved the myenteric nervous system itself in one case of enteric neuropathy [29]. In the last case (Guillain-Barré like syndrome with severe constipation), colon biopsies revealed a high number of lymphocytic follicles [31]. Immunohistochemical analysis demonstrated the presence of both CD4+ and CD8+ T-cells [29, 30, 33].

### 4. Discussion

Immune checkpoint inhibitors have shown promising results in cancers but can possibly induce auto-immune disorders. In this study, we reviewed the neurological adverse events occurring under immune checkpoint inhibitors in oncologic patients to more clearly define their incidence and characteristics.

The most striking feature of this literature review is the extremely broad spectrum of possible syndromes, potentially involving all areas of the central and peripheral nervous system. An over-representation of grade 1–2 neuropathies was reported with anti-PD1 antibodies, but this might be biased because most patients were suffering from advanced lung cancer and had received prior neurotoxic chemotherapy regimen. Clinical trials comparing anti CTLA-4 and anti PD-1 treatments did not show a different safety profile in terms of nAEs [4, 53]. In line with other organ immune-related adverse events, the median time of onset of nAEs after ICI treatments was started was 6 weeks. In the few cases in which histological analysis was carried out, lymphocytic infiltration was constantly found, strongly supporting an auto-immune disorder.

Severe nAEs (grade 3 and 4) appeared to be less common than other organs AEs, with an incidence slightly higher with anti-CTLA4 treatments (0.7%) than with anti-PD1 antibodies (0.4%). Surprisingly, when
considering all grades nAEs (grade 1–4), the reported incidence was higher with anti-PD1 than with anti-CTLA4 antibodies, but this difference might not be significant because most grade 1–2 nAEs consisted in subjective disorders, such as cephalalgia and dysgeusia. Cephalalgia, which is the most commonly AE reported (regardless of the grade), still represents 21% of the severe AEs. The mechanisms underlying these headaches are unclear and might be related either to non-neurological diseases such as hypophysitis or to undiagnosed meningitis.

This latter point underlines the need for standardised investigations to accelerate the management of potentially fatal adverse events. A decisional chart for neurological investigations can be proposed (Fig. 2). In case of clinical suspicion of encephalopathy, meningitis, meningoaradulitis or Guillain-Barré like syndromes, a lumbar puncture is probably the most useful investigation to support the relationship between the nAEs and the ICI treatment. Indeed, CSF abnormalities are almost constantly found, with an elevated proteins level associated to lymphocytic pleocytosis (except for Guillain-Barré like syndromes defined by an albuminocytological dissociation), thus supporting an inflammatory-mediated disease. In pure polyneuropathy, in which case CSF analysis might be deemed inappropriate, the differential diagnosis with other causes of neuropathy is made more difficult. In such cases, a demyelinating and/ or an asymmetrical pattern on electroneuromyography would be in favour of the relationship with ICI and should prompt to CSF analysis. Most of the time no auto-antibodies, including classical onco-neuronal antibodies usually seen in paraneoplastic syndromes [92], are identified. Only one recent article reported a case of encephalitis with anti-NMDA antibodies [93]. In myasthenic syndrome cases, nevertheless, the presence of serum anti-Ach Receptor antibodies was constantly found.

No standard treatment has yet been defined for neurological AEs. Clinical improvements have only been reported after the ICI drug discontinuation. Corticosensitivity is well documented in non-neurological immune-related AEs [94]. This seems to be also the case for nAEs, even in conditions where steroids are not usually recommended, such as Guillain-Barré syndromes. A commonly used protocol is oral prednisone around 1 mg/kg/day. A neurological AEs management algorithm has been proposed [78,95]. However, further studies are necessary to precise the framework in which they should be used, their dose and duration. Given the

Fig. 2. Simplified diagnostic algorithm for neurological investigations.
long half-life of anti-CTLA4 and anti-PD1 antibodies (3–4 weeks), maintaining steroids for at least 3 months seems logical. Other interventions such as immunosuppressive agents or plasmapheresis did not prove consistent efficacy and should be more carefully evaluated. Resuming ICI after neurological recovery is a matter of debate, and a careful analysis of the benefit/risk ratio should be done on a case by case basis. Prospective trials assessing the evolution of immune disorders after resuming ICI would be of value to clarify this issue.

Our study suffered from several limitations. The incidence of neurological AEs was extracted from large clinical trials, as it cannot be deducted from case reports. Unfortunately, cases in these trials were sometimes poorly characterised, or did not benefit from extensive explorations, which may have led to diagnosis misinterpretations. Regarding clinical characterisation, it is to be remembered that ICIs and especially anti-PD1 antibodies are recent drugs, with a relatively few number of cases described at the moment. Further descriptions will probably extend the understanding of the neurological AEs spectrum and will foster their optimal management.

Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.12.001.

References


