European Journal of Cancer 73 (2017) 1–8

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

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

S. Cuzzubbo [a,b,*], F. Javeri [a], M. Tissier [a], A. Roumi [a], C. Barlog [a,b], J. Doridam [a,b], C. Lebbe [c], C. Belin [a,b], R. Ursu [a,b], A.F. Carpentier [a,b]

[a] *Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Avicenne, Service de Neurologie, Bobigny, France*
[b] *Université Paris 13, UFR de Santé, Médecine et Biologie Humaine, Bobigny, France*
[c] *APHP Dermatology and CIC Departments, INSERM U976, Université Paris Diderot, Sorbonne Paris Cité, Hôpital Saint Louis, Paris, France*

Received 7 November 2016; accepted 6 December 2016
Available online 5 January 2017

KEYWORDS
Anti-PD1;
Anti-CTLA4;
Immune checkpoint inhibitors;
Neurological adverse events

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.

* *Corresponding author*: Service de Neurologie, Hôpital Avicenne, 125 rue de Stalingrad, 93009 Bobigny, France.
E-mail address: stefania.cuzzubbo@aphp.fr (S. Cuzzubbo).

http://dx.doi.org/10.1016/j.ejca.2016.12.001
0959-8049/

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, meningoradiculitis, 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 polyneuropathy), 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 meningoradiculitis 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