Autoimmune Encephalitis Related to Cancer Treatment with Immune Checkpoint Inhibitors: Systematic Review and Meta-analysis
(Protocol)

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1. BACKGROUND

Immune checkpoint inhibitors (CPI) have revolutionized the treatment of oncological patients and approved by the US Food and Drug Administration for the treatment of various cancers including unresectable malignant melanoma, non-small cell lung cancer, triple negative breast cancers and others (Darvin, Toor, Sasidharan Nair, & Elkord, 2018)(Yarchoan, Hopkins, & Jaffee, 2017).

Cancer cells evade immunosurveillance by activation of immune checkpoint pathways that lead to T lymphocytic Cell (TLC) apoptosis via the proteins: Cytotoxic T lymphocyte-associated Antigen 4 (CTLA-4), Programed Cell Death-1 protein (PD-1) and PD-1 Ligand (PD-L1). By inhibiting CTLA-4, PD-1 or PD-L1 it is possible to reinstate the antitumor response by the immune system and promote immune-mediated tumor cell elimination. (Darvin et al., 2018)(Dalakas, 2018)

With the success of CPI treatment there has followed an emerging evidence of increased risk of autoimmune diseases including autoimmune neurological adverse events (Larkin et al., 2017)(Johnson et al., 2019).

In 3,763 patients treated with CPI, 1 % experienced neurological adverse events and 0.2 % developed autoimmune encephalitis (Larkin et al., 2017). Another review of 48,653 treated with CPI found that 0.51 % developed autoimmune encephalitis/myelitis (Johnson et al., 2019). Although a rare complication, CPI-induced AIE is a potentially fatal condition posing a diagnostic challenge. Firstly the phenotype of CPI-induced AIE may differ from classical limbic encephalitis or NMDA-antibody encephalitis due to different disease-mechanisms and lack of detectable autoantibodies, and secondly it may be challenging to distinguish between CPI induced AIE and paraneoplastic induced AIE in cancer patients treated with CPI (Dalakas, 2018).

In general AIE pose a diagnostic challenge due to the delay of antibody testing in serum and cerebrospinal fluid (CSF) , but recently Graus et al. proposed a set of criteria for the diagnosis of AIE in which antibody diagnostic does not play a key role (Graus et al., 2016). The rapidly increasing use of CPI in antineoplastic treatment will most likely lead to an increased incidence of CPI-induced AIE, and clinicians will be

faced with the diagnostic challenges of this condition.

It is not known if CPI-induced AIE has a characteristic phenotype or is a heterogenic group, if AIE antibodies are present and if the proposed AIE criteria (Graus et al., 2016) are applicable to this new neurological entity. Thus we will therefore perform a systematic review, to our knowledge the first of its kind, in order to characterize the symptoms, clinical findings and laboratory results of presumed CPI-induced AIE.

1.1 Target condition

The target condition is AIE defined as subacute onset of working memory deficit, altered mental status or psychiatric symptoms in combination with either seizure activity, CNS focal deficits, CSF pleocytosis or MRI features suggestive of encephalitis, in patients treated with Nivolumab, Pembrolizumab, Atezolizumab, Ipilimumab or Durvalumab as monotherapy or combination. We will investigate the potential overlap with other CNS inflammatory conditions such as aseptic meningitis, cerebellitis or demyelinating disease with regards to clinical and laboratory findings.

In line with previous proposed criteria for AIE by Grauss. Et al (Graus et al., 2016), we will consider diagnosis of CPI-induced AIE as either: Possible encephalitis, definite limbic encephalitis, definite acute disseminated encephalomyelitis, probable or definite Anti-NMDA encephalitis and probable autoantibody negative encephalitis. We will categorize cases that do not fulfill any of the proposed criteria as “unlikely AIE”, and we will categorize cases where infectious or metabolic encephalopathy is not excluded as “not fully investigated”.

1.2 Index tests

The following will be considered as index tests: Cerebrospinal fluid (CSF) analysis for lymphocytes and autoantibodies, brain magnetic resonance imaging (MRI) and electroencephalography (EEG).

1.3 Rationale

The rationale for conducting a systematic review on the presumed autoimmune encephalitis related to treatment with anti-PD-1, anti-PD-L1 and anti-CTL-4 monoclonal antibodies is based on a growing number of cases reported. Investigating whether this heterogeneous group can be meaningfully classified into distinct subgroups (possible encephalitis, definite limbic encephalitis, definite acute disseminated encephalomyelitis, probable/definite Anti-NMDA encephalitis and probable autoantibody negative encephalitis), or if the conditions are multifaceted with overlapping pathophysiology, is an important first step for developing and evaluating an optimal treatment strategy.

2. OBJECTIVES

2.1 Primary objective

Using the PICO approach, we have phrased the following primary research question:

- In patients treated with an immune check point inhibitor (anti-PD-1, anti-PD-L1, and/or anti-CTLA-4) for disseminated malignancy, including systemic cancer, melanoma and hematologic malignancies, who develop rapidly progressive encephalopathy caused by brain inflammation and in the absence of an infectious cause **(P)**, are neurological examination and laboratory work-up including CSF analysis, EEG and brain MRI **(I)** compatible with a pure limbic encephalitis **(C)** or an encephalitis involving extra-limbic areas **(O)**?

2.2 Secondary objectives

In addition, we have phrased the following secondary research questions:

- In patients with immune check point inhibitor-associated encephalitis (ICI-AE) **(P)**, does plasma and cerebrospinal fluid work-up **(I)** for known autoimmune / paraneoplastic antibodies **(C)** reveal the presence of those antibodies **(O)**?

- Do patients with CPI-AIE **(P)** on the neurological examination and laboratory work-up **(I),** as compared to patients with non-CPI AIE **(C),** fulfill criteria for autoimmune encephalitis as proposed by Graus (Graus et al., 2016) **(O)**?

- Do patients with ICI-AE **(P)** treated with steroids, intravenous immunoglobulin (IVIG), plasma exchange (PEX), steroid-sparing agents (e.g. azathioprine) and monoclonal antibody-based immunotherapy and other immunomodulatory agents **(I)**, compared to patients with anti-NMDA receptor encephalitis (C), have a better, similar or worse prognosis regarding cognition, relapse and mortality **(O)**

3. METHODS

3.1 Criteria for considering studies for this review

3.1.1 Types of studies

We will evaluate all case reports, cross-sectional or longitudinal, retrospective or prospective observational studies as well as interventional trials, and, if available, meta-analyses and reviews, reporting on patient history of autoimmune encephalitis symptoms following treatment with anti-PD-1, anti-PD-L1 and anti-CTLA-4 monoclonal antibodies.

We will include only articles that allow assessment of patient data at the single-subject level. We will exclude articles that concern patients already used in another article by the same authors (or the same institution). We will include studies published in English and listed in Medline (PubMed), Cochrane Central Register of Controlled Trials (The Cochrane Library), and Embase without any date limit.

3.1.2 Participants

Adults (age ≥ 18 years) who have received anti-PD-1, anti-PD-l1 or anti-CTLA-4

monoclonal antibody therapies for disseminated cancer and diagnosed with AIE will be included. We will include patients irrespective of co-morbidities, concomitant therapies and previous history of CNS diseases.

3.2 Search methods for identification of studies

3.2.1 Electronic searches

We will search the following databases for relevant English literature with no date limit, and the search will be updated shortly before submission of the planned manuscript in order to include the newest references: Medline (PubMed), Cochrane Central Register of Controlled Trials (The Cochrane Library), and Embase.

We will use the following search terms including alternative spellings and MeSH: ("Checkpoint inhibitors" or "Antineoplastic Agents, Immunological" or "Nivolumab" or "Pembrolizumab" or "Atezolizumab" "Ipilimumab" or "Durvalumab" or "anti-PD-1" or "PD-1 inhibitor(s)" or "anti-PD-l1" or "PD-l1 inhibitor(s)" "anti-CTLA-4" or "CTLA-4 inhibitor(s)" and "encephalitis" or "meningitis" or "meningoencephalitis" or "cerebellitis" or "brain inflammation"). Non-English literature will be included only if an English abstract is available and a reliable translation of the manuscript into English is possible. The references of relevant articles will be manually searched to identify additional articles. Further, articles will be cross-referenced using the 'cited by' function on PubMed.

The search strategies PubMed, Cochrane and Embase (including MeSH terms in Pubmed and Cochrane and subject headings in Embase) will be saved and recorded in an appendix.

3.3 Data collection and analysis

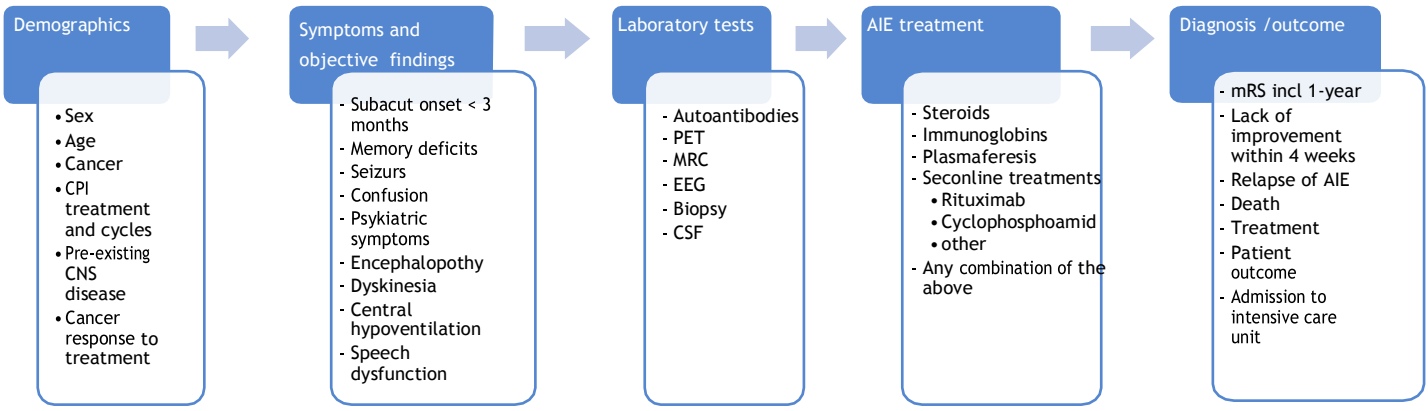
3.3.1 Selection of studies

A comprehensive literature search will be performed as outline above. Titles will be reviewed first, followed by evaluation of the abstracts with titles suggesting that a

study might be of relevance. Then eligible studies will be identified on the basis of their full text. Of note, we will only include studies that provide data on the single subject level (i.e. individual patients); thus, studies reporting solely on group level data will be excluded. The initial selection and further review will be performed by VN and OM. Disagreement on whether to include a study will be settled by LH. We will use proprietary reference manager software to manage the large number of studies, and we will document the study selection in a detailed flow chart.

3.3.2 Data extraction and management

Following identification of relevant studies, VN and OM will independently extract the relevant information from each study. We will record 1) journal name and Vancouver-style reference, 2) study design (e.g. systematic review, cross-sectional study, case report, cohort study), 3) method of recruitment (e.g. prospective or retrospective), 4) study setting, 5) characteristics of the patient population (e.g. age, gender, co-morbidities, cancer diagnosis, CPI therapy regime and cycles). More specifically, we will extract information related to the following categories; demographics, symptoms, neurological examination, laboratory tests, AIE treatment, diagnosis and outcome (details outlined in figure below). This information will be stored in a dedicated database. The review will be reported following the PRISMA criteria.



3.3.3 Assessment of methodological quality

We will assess the relevance and timing of the clinical and laboratory workup, as well as the conclusions that the authors arrive at. Also, we will assess whether the authors provide relevant discussions on differential diagnoses. Further, we will assess whether the studies declare the level of expertise of the physicians responsible for the diagnostic workup; neurologist specialized in CNS inflammation were consulted or in charge of the diagnostic workup.

3.3.4 Statistical analysis and data synthesis

Depending on the results of the literature search and review, we will propose to conduct a meta-analysis on available numerical data. If possible, odds ratios for laboratory tests on patients diagnosed with AIE will be performed.

3.4 Funding

None.

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