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Nephrotoxicity of immune checkpoint inhibitors in single and combination therapy. A systematic and critical review

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 January 2025 and was last updated on 15 January 2025.

INTRODUCTION

Review question / Objective To estimate the current incidence of nephrotoxicity in cancer patients treated with single and double ICI therapies.

Condition being studied The clinical use of the nine FDA-approved ICIs has expanded over more than nineteen different therapeutic indications (Seethapathy et al. 2021). Furthermore, combined ICI therapy poses a breakthrough in the treatment of some types of cancer such as non-small cell lung cancer and metastatic melanoma, in which concomitant administration of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) increases the response rate and survival (Larkin et al. 2015).
However, despite their innovative nature and the improvement in efficacy and safety, the use of these drugs has also unveiled a number of adverse events related to the immune system resulting from the boost in the immune response (Barquín-García et al. 2019). The incidence of adverse effects appears to be higher in patients receiving combined therapy compared to those receiving monotherapies, which would limit their use (Qiao et al. 2018).
Kidney injury is one of the complications observed. Although not the commonest, renal toxicity is a relevant complication associated to a poorer prognosis (Seethapathy et al. 2021). Acute kidney injury (AKI), proteinuria and electrolyte disorders are the main pathologies of the renal system associated with ICI treatment (Franzin et al. 2020) and the most common pathological lesion that leads to AKI is tubulointerstitial nephritis (90% of cases) (Cortazar et al. 2016). There are also other lesions associated with the autoreactivity of the

immune system such as glomerulonephritis (Cortazar et al. 2020).
Since the introduction of these drugs in 2011, the incidence of undesired renal effects has grown due to the increasing use and abundance of authorized ICIs, and the improved diagnosis (Isik et al. 2021). Updated knowledge on incidence may help guide decision making and optimize treatment.

METHODS

Participant or population Oncologic patients treated with ICIs.

Intervention Oncologic patients treated with ICIs that suffer kidney injury.

Comparator There is not comparative intervention.

Study designs to be included Retrospective studies.

Eligibility criteria Exclusion criteria: 1) preclinical studies, 2) reviews, protocols, communications and letters to the editor, 3) written in a language other than English, 4) full text not available and 5) studies evaluating the renal safety of combined therapies of ICIs with other antineoplastic drugs. Inclusion criteria: 1) clinical studies evaluating at least one ICI drug and 2) evaluating at least one kidney damage parameter: AKI or nephritis (independently for each ICI family).

Information sources Clinical studies published in Medline and the Web of Science databases.

Main outcome(s) The incidence of AKI was practically similar in the groups of anti-PD-1 (5.32%) and anti-PD-L1 (5.25%) but increased in patients treated with anti-CTLA-4 drugs (7.83%). Yet, it is noteworthy that ipilimumab had a higher incidence of AKI than tremelimumab (7.87% versus 4.35%, respectively). The higher incidence of AKI observed with ipilimumab may be related to the longer period of time that this drug has been used in clinical practice and the greater number of observational studies available (ipilimumab was the first ICI approved by the FDA in 2011, in contrast to tremelimumab, that was approved in 2022) (Research 2022, FDA). On the other hand, the incidence of AKI in the combined therapy group (anti-PD-1 + anti-CTLA-4) was 5.58%.
The mean incidence of nephritis in patients treated with anti-PD-1 did not exceed 1.5%. However, the clinical study carried out by O'Reilly et al. in 2019 reported an incidence of nephritis of 3.39% in patients treated with ipilimumab. In relation to the combined drug therapy (anti-PD-1 + anti-CTLA-4), the mean incidence of nephritis reaches values around 2%, although the study carried out by Tykody et al. in 2022 evidenced an incidence of nephritis in patients treated with nivolumab + ipilimumab of 3.85%.

Quality assessment / Risk of bias analysis Evaluation of the quality of clinical studies according to the standards of good clinical practice.

Strategy of data synthesis In each clinical study, percentage incidence of AKI and nephritis were calculated, according to the following formula:
Incidence (%)= (Number of cases (AKI or nephritis))/(Total number of patients) x 100.

Subgroup analysis The weighted mean and the standard error of the mean of AKI and nephritis incidence in ICI families and in anti-PD-1 + anti-CTLA-4 combination were also calculated. In addition, the weighted mean and the standard error of the mean of the incidence of the kidney damage parameters of nivolumab (anti-PD-1), pembrolizumab (anti-PD-1), atezolizumab (anti-PD-L1), durvalumab (anti-PD-L1), ipilimumab (anti-CTLA-4), tremelimumab (anti-CTLA-4), nivolumab + ipilimumab (anti-PD-1 + anti-CTLA-4), and pembrolizumab + ipilimumab (anti-PD-1 + anti-CTLA-4) were also calculated.

Sensitivity analysis Does not apply.

Country(ies) involved Spain - University of Salamanca.

Keywords Immune checkpoint inhibitors (ICIs); acute kidney injury; tubulointerstitial nephritis; nephrotoxicity; systematic review; cancer.

Contributions of each author

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