Endocrinología, Diabetes y Nutrición 69 (2022) 313–315

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

EDITORIAL

The role of immunotherapy in endocrine cancer treatment☆

Papel de la inmunoterapia en el tratamiento del cáncer endocrino

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Immunotherapy is considered the most significant advance in cancer treatment in recent decades. Immune checkpoint inhibitors (ICIs) have increased survival in patients with multiple neoplasms. They have changed the therapeutic paradigm by seeking to modify the relationship between the immune system and tumour cells and condition their response. Based on the theory of cancer immunoediting, which explains how neoplasms develop a phenotype that allows them to evade the immune system and influence the development of a more tolerant tumour microenvironment,[1] we can use antibodies, ICIs, to encourage activation and action of the CD8+ T lymphocyte against the tumour cell and reverse the immune evasion. We currently have antibodies against the membrane receptor for cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), against programmed cell death receptor 1 (PD-1) and against its ligand (PD-L1), receptors whose activation inhibits the immune response, and whose blockade has shown antitumour efficacy.

Lung carcinoma, squamous cell carcinoma of the head and neck, and of the urothelial tract and the liver, and melanoma, among others, are examples where we manage to modify the immune system's action, objectifying tumour responses, sometimes progressive, even after discontinuation of treatment, increasing overall survival. We have changed the objective of treating the tumour cell to treating the immune response. Since evasion of the immune system is a common principle in oncogenesis, it is plausible to reproduce its usefulness in endocrine neoplasia.

Endocrine neoplasms are an extremely heterogeneous group of tumours that originate in multiple organs, are heterogeneous in histology and biological in behaviour, often develop slowly and have a long natural history. Their heterogeneity and low incidence are an added difficulty in the development of new therapies, also for immunotherapy, currently under investigation with modest initial results, but with arguments for continuing with its development.

In the first place, because they are unexpected, the findings in pituitary carcinoma (PC) and in anaplastic thyroid carcinoma (ATC) stand out, with responses described in clinical cases and patients treated within studies of solid tumours. In PC, with only 10 published cases, responses have been observed both with anti-PD1 (pembrolizumab) and with the combination of anti-PD1 (nivolumab) and anti-CTLA-4 (ipilimumab).[2] Even considering a possible publication bias, the long duration of response in some cases, together with the finding of alterations in tumour repair genes in some

☆ Please cite this article as: Sánchez JC, Iglesias P. Papel de la inmunoterapia en el tratamiento del cáncer endocrino. Endocrinol Diabetes Nutr. 2022;69:313–315.

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patients treated and showing a response, justifies their potential usefulness in selected patients.

In patients with ATC, a neoplasm with no effective therapies, except for those with mutated BRAF, and with a very poor prognosis, we have data on activity in patients included in clinical trials. The anti-PD-1 spartalizumab achieved 19% objective responses in 42 ATC patients treated in a phase 1/2 trial in solid tumours, with a clear difference between PD-L1 positive patients (8/28; 29%) and PD-L1 negative patients (0/12; 0%).[3] This response to immunotherapy has been reproduced with pembrolizumab within a phase II trial in rare tumours, with a response rate of 18.8% in 16 treated ATC patients, and also in 10 patients treated within a phase 2 trial of anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab) used in combination, observing three lasting responses of even more than two years (30% objective response rate).[4] The findings described differ sufficiently from what is expected, given the natural history of these diseases, to consider the potential efficacy of immunotherapy in these diseases.

With moderate optimism, unlike for the results in ATC, we find results of ICIs in iodine-refractory differentiated thyroid carcinoma, with objective responses of 10% in the few patients included in clinical trials, leading to the development of immunotherapy combination trials with tyrosine kinase inhibitors (TKIs) that could optimise efficacy, are still without conclusive data. Regarding medullary thyroid carcinoma, we have information on very few patients and without clear efficacy results.

Another rare neoplasm in which modest antitumour activity of ICIs has been observed is adrenocortical carcinoma (ACC), both with the anti-PD-L1 antibody avelumab and with the anti-PD-1 pembrolizumab. The first was explored in a phase 1b trial in solid tumours, including 50 patients with ACC in pre-treated patients, at least progression to one line of systemic treatment (range 1–6) with 74% of the population treated with at least two lines, allowing them to continue with mitotane if they were previously receiving it. The trial reported a response rate of only 6%, which increased to 16.7% in PD-L1 positive patients, confirming the importance of understanding the biology underlying the immune response.[5] Pembrolizumab achieved similar results with response rates of 16% and 23% in two phase 2 studies in solid tumours that included 16 and 39 patients with ACC, suggesting a possible role of immunotherapy in this neoplasm.[6]

These conflicting results in different neoplasms are also observed in neuroendocrine tumours and carcinomas of different origins, as reflected in the systematic review carried out by Bongiovanni et al., which includes 14 published phase 1/2 trials evaluating treatment with ICIs (anti-PD -1, anti-PD-L1 and combinations of anti-PD-1 and anti-CTLA-4) in 636 patients with endocrine neoplasms (pancreatic, gastrointestinal, pulmonary and in other locations).[7] The response rate of 10% of the total number of patients cannot describe the benefit in such a heterogeneous population, both in the type of neoplasms and in the treatments used. Analysing the patients included in the different studies, more frequent responses are described in the groups of high-grade endocrine tumours or neuroendocrine carcinomas. To give an example, we can highlight a response rate of 20% with the anti-PD-1 toripalimab in neuroendocrine neoplasms (NEN) with a Ki-67 > 10%, and up to 42.9% in those patients with PD-L1 expression, or the difference observed between high-grade versus low-grade NEN responses reported in combination studies of anti-PD-1 and anti-CTLA-4.

Finding differences in the results obtained with immunotherapy in high- and low-grade NEN is consistent with the observations of differences in PD-1/PD-L1 expression, normally lower in low-grade tumours, the same as in tumour mutational load, higher in high-grade neoplasms and associated with the benefit of ICIs.[8]

These well-known examples show the importance of knowing the biology of tumours to improve the results of immunotherapy, not only in endocrine neoplasms, but also in oncology. The paradoxical results of immunotherapy in different tumours show that the choice of cancer treatment based on histological diagnosis is no longer enough. It is necessary to understand the immune system, the tumour microenvironment, and the relationships established between the different elements in the cycle of the immune response, because we will try to modify it.[9]

The first trials in patients using ICIs as a treatment for ATC or high-grade NEN suggest a possible future opportunity, probably related to a higher mutational load. However, phase I and phase 2 clinical trials with immunotherapy in endocrine tumours have generally shown limited results. While we cautiously await the development of ongoing clinical trials, we can conclude that the evidence of antitumour activity of immunotherapy in endocrine neoplasms provides the necessary proof of concept to investigate new strategies for patients in whom treatment with anti-CTLA-4/PD-1/PD-L1 does not obtain a response, identify new markers that allow an adequate selection of those to be treated, and the most appropriate therapy to ultimately redirect the immune response against the neoplasm of each patient.

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