



## CLINICAL CASE

Bilingual edition English/Spanish

### **Desensitization protocol to nivolumab without corticosteroid use in a kidney cancer patient**

### Protocolo de desensibilización a nivolumab sin corticoides en una paciente con cáncer renal metastásico

Sebastián Ramírez-Cruz<sup>1</sup>, María Amparo Lucena-Campillo<sup>1</sup>, Concepción Vila-Albelda<sup>2</sup>, María Garrido-Arévalo<sup>3</sup>, Lorena de Agustín-Sierra<sup>1</sup>, Benito García-Díaz<sup>1</sup>

<sup>1</sup>Servicio de Farmacia, Hospital Universitario Severo Ochoa, Leganés, Madrid, Spain. <sup>2</sup>Servicio de Alergología, Hospital Universitario Severo Ochoa, Leganés, Madrid, Spain. <sup>3</sup>Servicio de Oncología, Hospital Universitario Severo Ochoa, Leganés, Madrid, Spain.

#### **Author of correspondence**

Sebastián Ramírez Cruz  
Hospital Universitario Severo Ochoa.  
Servicio de Farmacia.  
Avenida de Orellana, s/n.  
28911 Leganés (Madrid), Spain.

Email:  
sebastianramir@gmail.com

Received 15 October 2019;  
Accepted 19 February 2020.

DOI: 10.7399/fh.11348

#### **How to cite this paper**

Ramírez-Cruz S, Lucena-Campillo MA, Vila-Albelda C, Garrido-Arévalo M, de Agustín-Sierra L, García-Díaz B. Desensitization protocol to nivolumab without corticosteroid use in a kidney cancer patient. Farm Hosp. 2020;44(4):182-3.

## Introduction

The immune system functions by using checkpoints that modulate T-lymphocyte activity and that can be activated by tumor cells to evade the immune response<sup>1</sup>. A new anticancer strategy employs immune checkpoint inhibitors (ICI), which reactivate the antitumor response mediated by T lymphocytes, thus releasing the immune checkpoint blockade in the tumor microenvironment<sup>1,2</sup>. Nivolumab is an ICI that binds to PD-1, blocking its interaction with PD-L1 and PD-L2<sup>1</sup>.

Desensitization protocols (DP) are strategies to allow the reintroduction of medications that induce hypersensitivity reactions in highly sensitized patients who need first-line therapies. These protocols involve the gradual administration of small amounts of the medication up to its total therapeutic dose. To increase the safety and tolerability of desensitization, patients are premedicated with different drugs that include systemic corticosteroids (SCS)<sup>3</sup>. In patients treated with ICIs, the administration of SCSs could adversely affect the therapeutic response due to their immunosuppressive effect. Therefore, it seems justified to avoid the use of SCSs in these patients<sup>2</sup>.

We describe a case study of a patient who experienced a hypersensitivity reaction to nivolumab. After she underwent a DP without corticosteroids, she safely received 20 doses of the drug.

## Case description

A 57-year-old woman, without known drug allergies, but with a medical history of high blood pressure, was diagnosed in April 2015 with stage IV clear-cell renal cancer, with bone and left adrenal gland metastases. She was started on pazopanib 800 mg daily, with stable disease until April 2017, when pulmonary progression was observed. She was started on cabozantinib 60 mg daily, with partial response. In February 2018, after new progression, she was started on nivolumab 3 mg/kg (249 mg) every two weeks. Ten minutes after starting the third infusion cycle, the patient began to exhibit erythema, bronchospasm, and dyspnea with an oxygen saturation of 89% and steady blood pressure. Infusion was stopped immediately, and hydrocortisone 100 mg and dexchlorpheniramine 5 mg were administered, with rapid improvement of symptoms. The Allergy Department performed skin tests (prick test and intradermo-reaction) with negative results.

Two weeks after the adverse event, the patient attended for a new cycle of nivolumab, using a PD stepped up speed. Premedication comprised orally administered cetirizine 20 mg, ranitidine 300 mg, and prednisone 60 mg the night before the cycle. Before starting infusion, the patient received intravenous dexamethasone 20 mg, ondansetron 8 mg, dexchlorpheniramine 5 mg, and ranitidine 50 mg. The Pharmacy Department compounded a

## KEYWORDS

Immunologic desensitization; Nivolumab; Corticosteroids; Kidney neoplasms.

## PALABRAS CLAVE

Desensibilización inmunológica; Nivolumab; Corticosteroides; Neoplasias renales.



single bag of nivolumab 249 mg diluted in 0.9% sodium chloride 249 mL. Based on indications provided by the Allergy Department, the rate of perfusion followed a rapid 15-step scheme subject to patient tolerance until completion of the total drug infusion (Table 1). This perfusion scheme, and an additional one 14 days later, were completed without adverse events.

In April 2018, in order to avoid possible unwanted interactions between the use of corticosteroids and immunotherapy, the Pharmacy Department suggested the possibility of developing a DP without corticosteroids. This DP was subsequently designed by the Allergy Department. Under the new protocol, premedication was given 24 hours and 1 hour before the initiation of the DP. Premedication comprised acetysalicylic acid 300 mg, ranitidine 300 mg, montelukast 10 mg, and cetirizine 20 mg. Prior to this cycle, treatment was discontinued due to suspicion of clinical progression. After radiological reassessment, brain metastases and a partial response at the extracerebral level were observed, and so DP to nivolumab without planned corticosteroids was resumed.

At the time of writing (May 2019), and after 20 administrations without any adverse effects, the patient remains in treatment with stable disease and with a good general condition.

## Discussion

Systemic corticosteroids induce apoptosis of effector T cells, altering memory T cells and regulatory T cells. One hypothesis suggests that, due to their mechanism of action, the immunosuppressive effect of SCSs could weaken the effectiveness of ICIs<sup>2,4</sup>. However, there are limited and contradictory data on the effect of the concomitant use of high doses of corticosteroids on the course of immunotherapy treatment.

A retrospective review of 210 patients with non-small-cell lung carcinoma (NSCLC) found that the group that was exposed to SCSs during the first nivolumab cycle had a lower response rate and shorter overall survival (OS) than those who did not<sup>2</sup>. A systematic review of SCS and ICI interactions did not come to a clear conclusion on interference between SCSs (type and dose) and immunotherapy, suggesting that the concomitant administration of SCSs and ICIs may not necessarily lead to worse clinical outcomes<sup>5</sup>. Another retrospective study in PD-(L)1-naïve patients with advanced NSCLC found that the initiation of SCSs during treatment with ICIs does not affect their efficacy, whereas the use of previously established SCSs remained associated with a worse response rate, decreased progression-free survival, and decreased OS. The prudent use of SCSs when initiating ICIs was recommended<sup>4</sup>.

We consider that it would be useful to design a DP that avoids the use of SCSs in premedication and uses prostaglandin blockers and/or leukotriene inhibitors given that the literature has provided examples of their safety and efficacy<sup>6,7</sup>. Our DP was simpler and shorter than traditional schemes because of the use of a single bag, which also guaranteed stability and minimized handling errors<sup>8</sup>.

## Bibliography

- Agencia Española de Medicamentos y Productos Sanitarios. Ficha técnica de nivolumab [Internet]. Madrid: Centro de Información de Medicamentos 2015 [accessed 13/05/2019]. Available at: [https://cima.aemps.es/cima/pdfs/ft/1151014002/FT\\_1151014002.pdf](https://cima.aemps.es/cima/pdfs/ft/1151014002/FT_1151014002.pdf)
- Scott SC, Pennell NA. Early use of systemic corticosteroids in patients with advanced NSCLC treated with nivolumab. *J Thorac Oncol.* 2018;13(11):1771-5. DOI: 10.1016/j.jtho.2018.06.004
- Sloane D, Govindarajulu U, Harrow-Mortelliti J, Barry WV, Hsu FI, Hong D, et al. Safety, costs, and efficacy of rapid drug desensitizations to chemotherapy and monoclonal antibodies. *J Allergy Clin Immunol Pract.* 2016;4(3):497-504. DOI: 10.1016/j.jaip.2015.12.019
- Arbour KC, Mezquita L, Long N, Rizvi H, Aucln E, Ni A, et al. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. *J Clin Oncol.* 2018;36(28):2872-8. DOI: 10.1200/JCO.2018.79.0006
- Garant A, Guilbault C, Ekmekjian T, Greenwald Z, Murgai P, Vuong T. Concomitant use of corticosteroids and immune checkpoint inhibitors in patients with hematologic or solid neoplasms: A systematic review. *Crit Rev Oncol Hematol.* 2017;120:86-92. DOI: 10.1016/j.critrevonc.2017.10.009
- Breslow RG, Caiado J, Castells MC. Acetysalicylic acid and montelukast block mast cell mediator-related symptoms during rapid desensitization. *Ann Allergy Asthma Immunol.* 2009;102(2):155-60. DOI: 10.1016/S1081-1206(10)60247-5
- Chung SJ, Kang SY, Kang RY, Kim YC, Lee KH, Kim TY, et al. A new non-dilution rapid desensitization protocol successfully applied to all-grade platinum hypersensitivity. *Cancer Chemother Pharmacol.* 2018;82(5):777-85. DOI: 10.1007/s00280-018-3662-0
- Vidal C, Méndez-Brea P, López-Freire S, Bernádez B, Lamas MJ, Armisén M, et al. A modified protocol for rapid desensitization to chemotherapy agents. *J Allergy Clin Immunol Pract.* 2016;4(5):1003-5. DOI: 10.1016/j.jaip.2016.05.015
- Sáenz de Santa María García M, Noguerado-Mellado B, Rojas-Pérez-Ezquerro P, Prieto-García A, Bartolomé-Zavala B, Tornero P. First case of allergy to nivolumab. *J Allergy Clin Immunol Pract.* 2017;5(4):1140-1. DOI: 10.1016/j.jaip.2017.01.015
- Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol.* 2008;122(3):574-80. DOI: 10.1016/j.jaci.2008.02.044

**Table 1.** Steps of the desensitization protocol. Single bag of nivolumab 1 mg/ml, nivolumab 249 mg in physiological saline 249 mL\*

Step	Time, min	Rate, mL/h	Dose, mg
1	15	0.1	0.025
2	30	0.2	0.050
3	45	0.4	0.100
4	60	0.8	0.200
5	75	1.5	0.375
6	90	3.0	0.750
7	105	6.0	1.500
8	120	12.0	3.000
9	135	24.0	6.000
10	150	40.0	10.000
11	165	60.0	15.000
12	180	90.0	22.500
13	195	125.0	31.250
14	210	150.0	37.500
15	250.25	180.0	120.750

\*Total dose administered: nivolumab 249 mg.

After a literature search of DP to nivolumab, we found a single case of a 14-step protocol using the classic three-bag scheme, which included SCSs in premedication<sup>9,10</sup>. However, we found no studies that addressed DP to immunotherapy without SCSs.

Our experience has demonstrated the safety of using a DP to nivolumab without SCSs, which did not compromise the effectiveness of treatment.

## Funding

No funding.

## Conflict of interest

No conflict of interests.

## Presentation at Congresses

An initial version of this paper was published as a communication at the 63rd SEFH Congress, Palma de Mallorca, Spain, 8-10 November 2018 (495. Desensitization protocol to nivolumab: a case study).