European Journal of Cancer 113 (2019) 72–74

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Letter to the Editor

Rechallenge of immune checkpoint inhibitor after pembrolizumab-induced myasthenia gravis

Billal Tedbirt [a,*], Michel De Pontville [b], Pierre Branger [c], Camille Picard [b], Barouyr Baroudjian [d], Céleste Lebbé [d,e], Antoine F. Carpentier [e,f], Julie Delyon [d,e] on behalf of the PATIO group

[a] Department of Dermatology, Rouen University Hospital, Rouen, France
[b] Department of Dermatology, Caen University Hospital, Caen, France
[c] Department of Neurology, Caen University Hospital, Caen, France
[d] Department of Dermatology, APHP Saint Louis Hospital, Paris, France
[e] Université Paris 7 Diderot, Sorbonne Paris Cité, Paris, France
[f] Department of Neurooncology, APHP Saint Louis Hospital, Paris, France

Received 23 February 2019; accepted 8 March 2019
Available online 12 April 2019

To the Editor,

We read with interest the article by Moreira *et al.* [1] entitled 'Myositis and neuromuscular side-effects induced by immune checkpoint inhibitors' in the January issue of *European Journal of Cancer*.

In this retrospective series, myositis was the most common neuromuscular immune-related adverse events (irAEs). Despite the risk of recurrent irAEs, rechallenging immune checkpoint inhibitors (ICIs) after discontinuation because of previous irAEs remains critical, when considering their potential benefits in terms of survival. Moreira *et al.* reported that one-third of patients after moderate symptoms of the skeletal muscles had reinduction of PD-1 inhibitor therapy. [1,2]. Myasthenia gravis (MG) is a serious and potentially fatal side-effect of ICIs [2,3]; only one case of MG was reported in this series, and to date, no case of ICI rechallenge after the occurrence of MG has been described. Here, we present a case of a patient who had ICI-induced MG and was treated with nivolumab because of melanoma progression (Fig. 1).

A 77-year-old patient diagnosed with BRAF wild type stage IV melanoma received the anti–programmed cell death protein 1 pembrolizumab as first-line treatment. After the fourth infusion, the patient gradually developed visual disorders and dysphagia. Clinical examination found bilateral ptosis and motor deficiency during repeated bending. The creatine kinase level remained normal during the whole follow-up. Acetylcholine receptor–binding antibody and antibodies against muscle-specific tyrosine kinase were negative. Brain magnetic resonance imaging and lumbar puncture were normal. Electromyography (EMG) showed a significant decrement without postexercise facilitation in the tongue, left nasalis and orbicularis oculi. These results were consistent with the diagnosis of MG secondary to pembrolizumab therapy. He was successfully treated and cured with intravenous immunoglobulin

DOI of original article: https://doi.org/10.1016/j.ejca.2018.09.033.
* *Corresponding author:* Dermatology Department, Rouen University Hospital, 1 rue de Germont, 76031 Rouen Cedex, France. Fax: +(33) 232 88 88 55.
E-mail address: billal.tedbirt@etu.univ-rouen.fr (B. Tedbirt).

https://doi.org/10.1016/j.ejca.2019.03.006

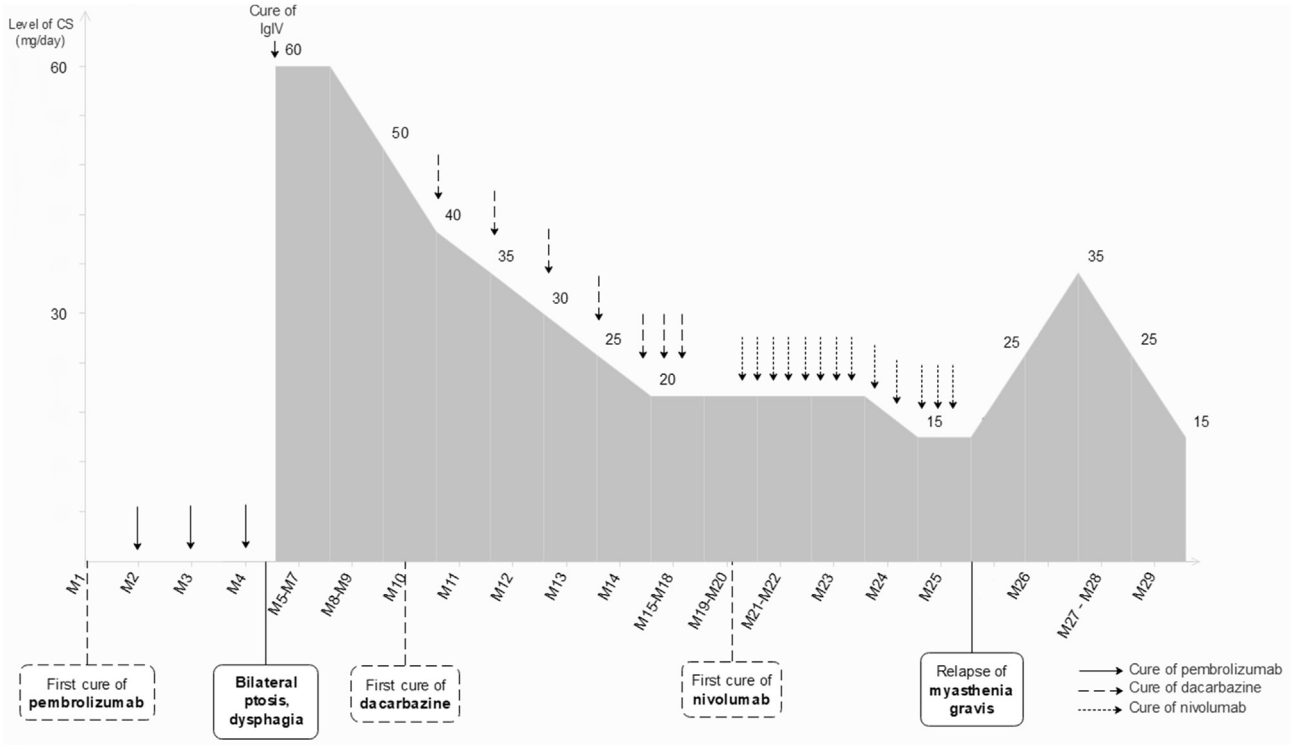

Fig. 1. Timeline of the patient. IgIV, intravenous immunoglobulin; CS, corticosteroid.

(0.4 g/kg/day for five days) and pyridostigmine bromide (360 mg/day) associated with prednisone therapy at a dose of 1 mg/kg/day (i.e. 60 mg per day). Pembrolizumab therapy was discontinued; melanoma was in partial response.

Five months after stopping pembrolizumab, metastatic melanoma lymph node relapsed. The patient received dacarbazine as a second line of treatment for 6 months, until tumour progression. As no other therapeutic option was available, anti–PD-1 therapy with nivolumab at the dose of 3 mg/kg every 2 weeks was started; pyridostigmine bromide and corticosteroid therapy at the dose of 20 mg per day were preventively associated.

At 3 and 6 months after starting nivolumab, positron-emission tomography–computed tomography showed a partial metabolic response, and no recurrence of MG occurred. However, after fourteen nivolumab infusions, a recurrence of diplopia and dysphagia was reported at the dose of 15 mg of corticosteroid, suggesting a recurrence of the myasthenic syndrome. Corticosteroid was gradually increased to 35 mg per day with a good response on MG-related symptoms. Nivolumab was discontinued; after 3 months of follow-up, melanoma remained in partial response.

MG is a rare neurological disorder induced by ICI and occurs below 1% of patients. [4]. Symptoms of MG appear between 7 and 11 weeks after initiation of treatment. [3,6,7]. MG may appear de novo or be present before initiation of treatment. [6,7]. Diagnosis is made by neurological examination, ice pack and edrophonium tests, serum test and EMG. The specific autoantibodies are rarely positive in ICI-induced MG. [8]. Despite the risk of recurrent irAEs, this case suggests that rechallenging ICI after discontinuation due to previous MG can be partially safe under careful clinical monitoring and adaptation of the corticosteroid dosing.

Source of funding

None.

Conflict of interest statement

J.D. reports travel accommodations from Pierre Fabre. C.L. reports consulting or advisory role for Roche, BMS, MSD, Amgen and Novartis. A.F.C. reports consulting or advisory role for BMS. M.D.P. reports consulting or advisory role for BMS, MSD and Roche. B.B. reports honoraria from BMS and MSD. The other authors have no conflict of interest to declare.

References

[1] Moreira A, Loquai C, Pföhler C, et al. Myositis and neuromuscular side-effects induced by immune checkpoint inhibitors. Eur J Canc 2019;106:12–23.

[2] Delyon J, Brunet-Possenti F, Leonard-Louis S, et al. Immune checkpoint inhibitor rechallenge in patients with immune-related myositis. Ann Rheum Dis September 2018. https://doi.org/10.1136/annrheumdis-2018-214336.

[3] Zimmer L, Goldinger SM, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Canc 2016;60:210–25.
[4] Cuzzubbo S, Javeri F, Tissier M, et al. Neurological adverse events associated with immune checkpoint inhibitors: review of the literature. Eur J Canc 2017;73:1–8.
[6] Lau KHV, Kumar A, Yang IH, Nowak RJ. Exacerbation of myasthenia gravis in a patient with melanoma treated with pembrolizumab. Muscle Nerve 2016;54(1):157–61.
[7] Nguyen BHV, Kuo J, Budiman A, Christie H, Ali S. Two cases of clinical myasthenia gravis associated with pembrolizumab use in responding melanoma patients. Melanoma Res 2017;27(2):152–4.
[8] Shirai T, Kiniwa Y, Sato R, et al. Presence of antibodies to striated muscle and acetylcholine receptor in association with occurrence of myasthenia gravis with myositis and myocarditis in a patient with melanoma treated with an anti-programmed death 1 antibody. Eur J Canc 2019;106:193–5.