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Letter to the Editor

Neurotoxicity induced by targeted therapies in patients treated for metastatic melanoma

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Dear Editors,

Targeted therapies (TTs) have improved the management of advanced BRAF-mutated melanoma, specifically BRAF inhibitors (BRAFi) such as vemurafenib and dabrafenib combined with MEK inhibitors (MEKi): such as cobimetinib and trametinib, respectively, and more recently the combination of encorafenib with binimetinib [1,2]. The most common adverse events reported with TT are arthralgia, rash, alopecia, photosensitivity and fatigue [1,3].

We hereby describe seven cases of neuropathy under TT. Clinical data are summarised in Table 1.

Seven patients were treated for stage IV metastatic melanoma (MM) (N = 3) or in adjuvant setting after complete lymph node dissection (N = 4). Dabrafenib and trametinib were used in six cases and vemurafenib in the last patient. The mean delay between initiation of TT and the onset of neurological symptoms was 9.9 months (range 3–26 months). Five patients developed sensorimotor polyneuropathy (in three cases, polyneuropathy was non-length dependent [LD]). One had a sensory axonal neuropathy LD, and the last patient had a recurrence of a preexistent sensorimotor chronic inflammatory demyelinating polyneuropathy.

Treatment was discontinued in six cases. In one case (patient 4), vemurafenib was continued for 9 months, before being stopped because of worsening of the symptoms: severe sensorimotor polyneuropathy LD. All other diagnoses potentially responsible of neurological symptoms were excluded: metastatic evolution, meningeal carcinomatosis and bacterial or viral meningitis. After discontinuation of TT, three patients had a progressive amelioration of the neurologic status followed by disappearance of symptoms in 10–14 months. Despite withdrawal of treatments, one patient required prolonged reeducation and remained with moderate sensorimotor defects (14 months later) and another one had a stable persisting neuropathy (still present after 10 months). Two patients with severe neurotoxicity improved their symptoms with high-dose steroids (1 mg/kg), tapered within 1–3 months; two other patients

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Table 1
Clinical data of patients who developed or had worsened neurotoxicity under targeted therapies.

Case number	Age (years)	Sex	Melanoma	Treatment	Delay before neurotoxicity	Type of neuropathy	Treatment	Evolution after discontinuation • Neuropathy • Melanoma
			AJCC stage		(months)	Grade (CTCAE)		
1	72	W	Stage IV BRAF V600E	D+T	4	Sensory axonal polyneuropathy, LD Grade I	Stop combined therapy Symptomatic treatment (pregabalin, clonazepam)	• Rechallenge 30 months later (2017) with V+C: within 4 months: recurrence of neuropathy • Evolution of melanoma within one year treated by pembrolizumab, ipilimumab and exclusive palliative care 2 years later
2	50	M	Stage III BRAF V600K	D+T (adjuvant)	6	Sensory and motor polyneuropathy, ataxia, non-LD Grade II	Stop combined therapy Symptomatic treatment (pregabalin, clonazepam) + IV Ig (2 cycles, stopped after pulmonary emboly)	• Progressive improvement of symptoms • Melanoma in remission with 3 years of follow-up
3	60	M	Stage IV BRAF V600E	D+T	16	Sensory and motor polyneuropathy non-LD Grade II	Stop combined therapy Symptomatic treatment (pregabalin, clonazepam)	•Persistence of neuropathy grade I •Cerebral evolution within 8 months treated by radiotherapy, complete response after 3 years of follow-up
4	75	W	Stage IV BRAF V600E	V	26	Sensory polyneuropathy 8 months later, worsening under V: severe sensory and motor polyneuropathy LD: stop V Grade III	Stop V, 9 months after the first symptoms and CTC tapered within 1 month	• Progressive improvement but still under rehabilitation with hypoesthesia, and difficulty in walking • Complete response after 3 years of follow-up
5	69	M	Stage III BRAF V600E	D+T (adjuvant)	9	Sensory and motor polyneuropathy non-LD Grade III	Stop D+T Treatment CTC tapered within 3 months	• Stabilisation • Cerebral evolution within 3 months treated by radiotherapy and lymph node evolution treated by pembrolizumab, in progress, 8 months later
6	55	M	Stage III BRAF V600E	D+T (adjuvant)	5	Sensory and motor polyneuropathy Grade II	Stop D+T No treatment for neuropathy	• Improvements in motor symptoms but persistence of very mild sensory neuropathy • Melanoma in remission after 3.5 years of follow-up
7	54	M	Stage III BRAF	D+T (adjuvant)	3	Recurrence of preexistent sensory and motor chronic inflammatory demyelinating polyneuropathy Grade II	Stop D+T Treatment: IV Ig (5 cycles)	• Mild sensitive neuropathy remains, normal motor function • Melanoma in remission after 8 months of follow-up

W: woman, M: man, V: vemurafenib (960 mg twice daily), C: cobimetinib (60 mg per day), D: dabrafenib (150 mg twice daily), T: trametinib (2 mg per day), IV Ig: intravenous immunoglobulin, CTC: corticosteroids, CTCAE: Common Terminology Criteria for Adverse Events Version 4.0, LD: length dependent, AJCC: American Joint Committee on Cancer.

received intravenous immunoglobulin in addition to steroids and improved. The other two were treated with antalgic and symptomatic medications such as pregabalin and clonazepam. One patient who did not receive any symptomatic treatment had improvement of his motor symptoms but persistence of a mild sensory neuropathy.

A reintroduction test was carried out in one patient 30 months after interruption of dabrafenib and trametinib with the introduction of vemurafenib and cobimetinib. The relapse of the neuropathy was observed with the same delay as the first time, that is, 4 months after the initiation of TT treatment. TTs were then definitively stopped.

Three patients had a melanoma progression after discontinuation (within 3–12 months), and four patients were in complete response and off TT with a follow-up between 8 months and 3.5 years.

1. Discussion

We report six cases of polyneuropathies and one case of recurrence of a chronic polyneuropathy in patients treated with TT for melanoma.

Oncogenic mutations in BRAF are found in approximately 40–50% of melanomas and result in constitutive activation of the mitogen-activated protein kinases pathway (MAPKp) [4–7]. The association BRAFi and MEKi have improved the outcome of patients with MM [8]. Some adverse events are common with BRAFi and MEKi drug classes: rash, fatigue, joint pain, diarrhoea and rash, whereas others appear to be specific to an agent such as photosensitivity for vemurafenib and fever for dabrafenib [1,3]. These drugs are still relatively recent, and all toxicities are not yet described nor well known. Here, we report six cases of neuropathy and one recurrence of a chronic polyneuropathy associated with TT. Very few cases of patients with neurological toxicity under TT have been reported in the literature so far. A case of polyneuropathy is reported in one patient treated with radiotherapy and concomitant BRAFi therapy [9], and three cases of facial palsy have been reported with vemurafenib [10,11]. Two cases of Guillain-Barre–like syndromes have been reported with both regimens of TT and one after dabrafenib, respectively [12,13].

The mechanisms underlying these neurological effects are still hypothetical. Some authors postulated that they could be secondary to a paradoxical activation of the MAPKp, resulting in the proliferation of Schwann cells [14]. Indeed, selective activation of MAPK signalling or, alternatively, overexpression of RAF was shown to negatively impact Schwann cell differentiation [15]. The apparent therapeutic benefit of systemic steroids can also suggest that an aberrant immune activation may contribute to such neurologic manifestations [16] especially because MAPKp is known to play a crucial role in the production of proinflammatory cytokines.

Development of TT-associated neurotoxicity can be very severe [17]; one patient in our series is still recovering and disabled. In five cases, neurotoxicity consisted in sensory and motor polyneuropathy non-LD (3 cases) with ataxia. Prompt management is required after all others diagnoses have been ruled out by complete clinical examination, laboratory work and imaging. Other drugs known to be responsible for sensory or motor neurotoxicity should also be considered.

In our patients, discontinuation of the treatment allowed complete recovery when performed early after the onset of symptoms. In one patient, treatment was continued for 9 months after the onset of neurologic symptoms, which was associated with a symptomatic aggravation and a severe neurotoxicity, highlighting the potential importance of a rapid interruption of the TT treatment. Management in our series consisted on symptomatic treatment and corticosteroids or intravenous immunoglobulins in cases of severe staging. Corticosteroids were tapered in accordance to resolution of neurologic symptoms.

One patient developed neurotoxicity with both regimens of TT, which suggests this side effect is a class effect driven by MAPKp interruption and not specific to a particular drug. Based on this case, reintroduction of distinct association of BRAFi and MEKi should be extremely cautious in case of neurotoxicity. In six of our patients who were treated with the BRAFi and MEKi combination, it is not possible to clearly determine the respective roles of BRAFi or MEKi in the mechanism of the neurologic toxicity. In one patient who developed this toxicity under vemurafenib monotherapy, we can be sure of the responsibility of vemurafenib only. Some cases were more clearly associated with MEKi [12] and others related to BRAFi [13].

Three patients had a MM progression after discontinuation, three patients were still stage III, and only one patient was still on complete response. With this small number of patients, we cannot assess any relationship between neurologic toxicity a clinical benefit to TT.

Based on the patient who presented a recurrence of a chronic polyneuropathy and on the case of Taha *et al.*, we recommend physicians to be extremely cautious with such patients regarding reintroducing TT [12].

Reporting such rare and potentially severe neurotoxicity is of critical importance for several reasons. First, it will help to guide early management of the patients presenting this adverse event. Second, it should also be a strong incentive for other colleagues to report such cases to better evaluate the real incidence of TT-associated neurotoxicity and to perform further work to understand the underlying pathophysiology of these manifestations. Finally, many patients, especially those treated for metastatic melanoma, will also receive checkpoint inhibitors before or after TT or even in

association with TT. Immune checkpoints are well known to induce rare neurological adverse events that are similar to those TTs reported here [18]. It is, therefore, very important to know that both strategies of treatment can result in neurotoxicity and not systematically consider that immunotherapy is the responsible treatment.

Conflict of interest statement

C.R. has acted as a consultant of BMS, Pierre Fabre, Merck, Novartis and Roche. C.M. has acted as a consultant of Roche, Novartis, BMS and Merck. E.R. has acted as a consultant of BMS and Roche. Others declare no competing interests.

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