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Reintroduction of immune-checkpoint inhibitors after immune-related meningitis: a case series of melanoma patients

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ABSTRACT

Immune-checkpoint inhibitors (ICIs) targeting cytotoxic T lymphocyte-associated antigen-4 and programmed cell death ligand-1) are associated with several immune-related neurological disorders. Cases of meningitis related to ICIs are poorly described in literature and probably underestimated. Several guidelines are available for the acute management of these adverse events, but the safety of resuming ICIs in these patients remains unclear. We conducted a retrospective case series of immune-related meningitis associated with ICIs that occurred between October 1 2015 and October 31 2019 in two centers: Saint-Louis and Cochin hospitals, Paris, France. Diagnosis was defined by a (1) high count of lymphocytes (>8 cells/mm3) and/or high level of proteins (>0.45 g/L) without bacteria/virus or tumor cells detection, in cerebrospinal fluid and (2) normal brain and spine imaging. Patients were followed-up for at least 6 months from the meningitis onset. Seven cases of immune-related meningitis are here reported. Median delay of meningitis occurrence after ICIs onset was 9 days. Steroid treatment was introduced in four patients at a dose of 1 mg/kg (prednisone), allowing a complete recovery within 2 weeks. The other three patients spontaneously improved within 3 weeks. Given the favorable outcome, ICIs were reintroduced in all patients. The rechallenge was well tolerated and no patients experienced meningitis recurrence. In conclusion, in our series, the clinical course was favorable and steroids were not always required. Resuming ICIs in these patients appeared safe and can thus be considered in case of isolated meningitis. However, a careful analysis of the risk/benefit ratio should be done on a case-by-case basis.

INTRODUCTION

Immune-checkpoint inhibitors (ICIs) targeting cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1) and PD ligand 1 are today a standard of care in the treatment of several cancers. Initially approved for unresectable metastatic melanoma and non-small cell lung cancer, ICIs are now increasingly used to treat a high variety of solid-organ and hematological cancers. They are nevertheless associated with several immune-related (ir) disorders that can potentially involve every organ or system but gastrointestinal, dermatological, hepatic, endocrine and pulmonary toxicities predominate.[1] Neurological ir adverse events (irAEs-N) are rare, with an overall incidence of 3.8% for anti-CTLA4 antibodies, 6.1% for anti-PD1 antibodies and 12.0% for the combination of them. However, the incidence of severe irAEs-N is below 1% for all types of treatment. Although rare irAEs-N require prompt recognition and treatment to avoid substantial morbidity.[2 3] Several guidelines are available for the acute management of irAEs,[4] but their long-term management is less standardized. Specifically, no clear data are available on the safety of resuming ICIs after an irAE. Some studies reported a 40%–60% rate of recurrence of the specific or distinct AE after the reintroduction of ICIs.[5–8] As a consequence, only few patients with irAEs-N resume ICI treatment in current practice because of life-threatening risk related to neurological syndromes.

Given the benefits of ICI therapy in patients with cancer, additional research is necessary to guide clinicians in practical decisions. Considering the heterogeneity of irAEs, even within neurological irAEs, recommendations for resuming ICIs should be specifically defined for each type of them. Herein, we report a retrospective series of seven consecutive patients who developed ir-meningitis with the aim of defining the long-term management and exploring the safety of ICIs reintroduction in these patients.

METHODS

We collected the cases of ir-meningitis associated with ICIs in adult melanoma patients of Saint-Louis and Cochin hospitals, Paris, between October 1 2015 and October 31

Table 1 Demographic and clinic characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex, age (years)	M, 71	F, 29	F, 51	F, 46	F, 64	M, 27	F, 20
Stage of melanoma BRAF status	IIIb V600E mutant	IIIc Wild type	IV V600E mutant	IV Wild type	IIc Wilde type	IIIc Wild type	IV V600E mutant
ICI regimen at the irAE-N onset	Nivolumab 3 mg/kg	Ipilimumab 1 mg/kg +nivolumab 3 mg/kg	Spartalizumab 400 mg/28 days	Ipilimumab 1 mg/kg +nivolumab 3 mg/kg	Nivolumab 3 mg/kg	Ipilimumab 3 mg/kg +nivolumab 1 mg/kg	Ipilimumab 3 mg/kg+nivolumab 1 mg/kg
Concomitant cancer treatment	0	0	Dabrafenib, Trametinib	0	0	0	0
No of ICI doses before irAE-N	1	1	4	2	1	2	1
Delay of neurological symptoms onset from ICI onset (days)	6	6	95	50	6	9	17

F, female; ICI, immune-checkpoint inhibitor; irAE-N, neurological immune-related adverse event; M, male.

2019. Saint-Louis patients were registered in MelBase, a French clinical database with biobank dedicated to the prospective follow-up of adult patients with advanced melanoma. MelBase protocol was registered in the NIH clinical trials database (NCT02828202). Written informed consent was obtained from all patients.

Diagnosis was defined by the association of (1) a clinical pattern compatible with meningitis; (2) >8 lymphocytes/mm^3 and/or protein level >0.45 g/L in cerebrospinal fluid (CSF), without bacteria/virus or tumor cells detection; (3) normal brain/spine imaging. Patients were included in this study if followed by a neurologist for at least 6 months after meningitis occurrence. The decision of ICI reintroduction was made on a case-by-case basis.

We collected patients demographics and ir-meningitis characteristics. IrAEs were defined using the National Cancer Institute Common Terminology Criteria for Adverse Events, V.4.03.[9] Duration of corticosteroids was collected, and patients were considered 'off steroids' when hydrocortisone equivalent dose was ≤30 mg/day. We also collected tumor evaluations according to the ir-response criteria[10] at 3 months after the ICI readministration and at the latest follow-up.

RESULTS

We, here, report seven consecutive cases of ir-meningitis. Table 1 summarizes demographic and clinical characteristics of patients. Median delay of meningitis onset after the first dose of ICI was 9 days (range: 6–95 days). CSF study displayed lymphocytic meningitis in six out of seven patients, and an isolated high protein level in patient 5, but lumbar puncture was realized 45 days after the onset of neurological symptoms in this patient. CSF microbiological studies were negatives in all patients and no evidence of tumor meningitis was found in CFS study or brain and spine MRI. MRI did not find any signs of myelitis nor encephalitis, and therefore, a diagnosis of isolated ir-meningitis was made.

After diagnosis of ir-meningitis, a steroid treatment (prednisone 1 mg/kg) was introduced in patients 1, 2, 4 and 6 (all with irAEs-N ≥grade 2), allowing a complete clinical recovery within 2 weeks. After 1-2 weeks of full dose, corticosteroids were gradually tapered until discontinuation after 6 weeks. The other three patients (all with grade 1 AEs) spontaneously improved within 3 weeks (table 2).

Given the favorable outcome of ir-meningitis, ICI treatment was reintroduced in four patients (cases 2, 3, 5, 7) after 4–54 days from irAE-N. For the other three patients, despite a quick recovery of meningitis, ICI was not resumed immediately because of the high grade of nAE (grade 3) in patient 1, and of multiple co-occurring non neurological irAEs in patients 4 and 6. These patients were followed by whole body imaging every 3 months and ICIs were reintroduced at time of disease progression.

The rechallenge was well tolerated in six out of seven cases: no meningitis nor other irAEs occurred. Patient 3 developed a severe interstitial lung disease, without meningitis recurrence, leading to permanent discontinuation of ICI treatment (table 3). Table 3 shows the cancer status at 3 months from the rechallenge of ICIs and at the latest follow-up.

DISCUSSION

A broad spectrum of neurological irAEs has been described in the literature, potentially involving all areas of the central and peripheral nervous system.[2 11] Cases of ir-meningitis have been less frequently reported. However, their frequency is likely underestimated because their presentation can be paucisymptomatic. The occurrence of an unusual headache during ICI treatment should raise the suspicion of meningitis and lead to appropriate

Table 2 Characteristics of ir-meningitis and management with steroids

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Severity grade of meningitis	3	2	1	2	1	2	1
Symptoms	Fever, confusion, partial seizure.	Headache, nausea, photophobia.	Headache, four limbs pain.	Headache, vomiting.	Headache, vomiting.	Headache, fever.	Fever, headache
Lumbar puncture							
cells/mm^3	40 (90% L)	8 (100% L)	19 (90% L)	25 (90% L)	0	9 (90% L)	320 (90% L)
Protein level	0.99 g/L	0.30 g/L	0.39 g/L	0.43 g/L	0.59 g/L	0.54 g/L	<0.45 g/L
Steroid treatment*							
Initial dose	1 mg/kg/day	1 mg/kg/day	0	1 mg/kg/day	0	1 mg/kg	0
Length at full dose	7 days	7 days		7 days		14 days	
Length of tapering	42 days	42 days		42 days		42 days	
Delay of complete recovery							
From irAE-N onset	18 days	17 days	10 days	21 days	65 days	49 days	10 days
From steroids onset	2 days	14 days	–	2 days	–	14 days	–
Other irAEs occurrence	None	None	None	Hypophysitis (gr. 2), diabetes (gr. 2), hepatitis (gr. 1)	None	Hypophysitis (gr. 2), hepatitis (gr. 4), colitis (gr. 2) small fibers neuropathy (gr.1)	None

*Prednisone equivalent doses.
irAE, immune-related adverse event; irAE-N, neurological immune-related adverse event; L, lymphocytes.

investigations. Notably, differential diagnosis with bacterial/viral meningitis and meningeal carcinomatosis must be considered in first place, hence lumbar puncture and brain/spine MRI with and without contrast generally lead to the correct diagnosis.

As reported for other irAEs-N, we did not observe any exclusive association between ir-meningitis and a class of ICIs.[2 8] Clinical signs of meningitis occurred early with a median delay of 9 days after the ICI onset and a median number of ICI cycles of 2, compared with 6 weeks and three cycles observed in all kinds of irAEs-N respectively.[2 8] Ir-meningitis had a favorable evolution with a fast and full recovery in all patients. According to published recommendations,[12] steroid treatment was introduced in more severe cases (grade ≥2) and maintained at full dose (prednisone 1 mg/kg/day) for one or 2 weeks depending on the clinical recovery of meningitis and then tapered over 6 weeks given the half-life of ICI drugs.

The safety of ICI reintroduction after an irAE is still a matter of debate. Some studies showed a quite poor tolerance of resuming ICI after a severe irAE, reporting an occurrence of the same or a distinct AE in 40%–55% of patients.[5–7] The risk of irAEs-N recurrence is likely similar to other ir-AEs, but, very few cases of reintroduction of ICIs after an irAE-N have been reported so far, probably because of concerns on potential severity and life-threatening risk associated to irAEs-N. Dubey *et al* reported a series of 10 patients retreated with ICIs after a severe irAEs-N. The irAE-N recurrence rate was 60% and the authors suggested a correlation with a short steroid treatment (less than 2 weeks) after the initial AE in these patients.[8]

Only few cases of ICI rechallenge after an ir-meningitis are reported in literature. Spain *et al* reported a melanoma patient with meningitis associated with ir-hepatitis. The rechallenge with the same regimen resulted in severe ir-colitis.[13] Fellner *et al* reported another case of reintroduction of ICIs after meningitis related to ipilimumab–nivolumab combination therapy. In this case, only nivolumab was resumed, with a good tolerance.[14] In both cases, ICI drugs were reintroduced at the moment of cancer recurrence according to checkmate-067 trial results, in which 68% of patients who discontinued ICI treatment due to toxicity experienced a long response (median time of 13 months).[15]

In our series of seven consecutive patients, ICI treatment was early reintroduced in four patients (all with irAE-N grade ≤2), as soon as the meningitis symptoms had completely recovered. Tolerance of reintroduction was good in three out of four patients. One patient

Table 3 Tolerance of ICI reintroduction

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Delay of resumption of ICI after meningitis (days)	373	54	24	118	4 (No ICI discontinuation)	126	19
ICI regimen at the rechallenge	Ipilimumab 1 mg/kg +nivolumab 3 mg/kg	Ipilimumab 1 mg/kg +nivolumab 3 mg/kg	Spartalizumab 400 mg	Nivolumab 3 mg/kg	Nivolumab 3 mg/kg	Spartalizumab 400 mg +ribociclib 600 mg/day	Nivolumab 3 mg/kg
Steroid treatment at the time of ICI resumption*	0.5 mg/kg/day	0	0	0	0	0	0
Meningitis recurrence	No	No	No	No	No	No	No
Other irAEs occurrence at rechallenge with ICIs	No	No	Interstitial lung disease (grade 3)	No	No	No	No
Cancer status at 3 months from rechallenge with ICIs	PD	PR	PD	PD	PR	PD	PR
Cancer status at latest follow-up (months from rechallenge)	Death caused by cancer progression	Maintained CR (32 months)	Maintained PR (25 months)	Death caused by cancer progression	Maintained PR (6 months)	Death caused by cancer progression	Maintained PR (17 months)

*Prednisone equivalent doses.
CR, complete response; ICI, immune-checkpoint inhibitor; irAE, immune-related adverse event; PD, progression disease; PR, partial response.

developed a severe non-neurological irAE (interstitial lung disease) leading to permanent discontinuation of ICI treatment. In the three other cases, ICI reintroduction was differed at the time of disease progression since ir-meningitis was more severe or associated with other irAEs. In cases of multiple irAEs, dual therapy was shifted to anti-PD1 monotherapy regimen. The reintroduction was well tolerated in all cases: no patients experienced a recurrent or new irAE.

CONCLUSIONS

Cases of meningitis related to ICIs are poorly described in literature. In our cases, the clinical course was favorable and steroids were not always required. In case of isolated ir-meningitis, an early reintroduction of ICI treatment at the same regimen appears to be safe, even in case of combination therapy (anti-CTLA-4/PD-1). On the contrary, a longer discontinuation of ICI drug (until disease progression) and a regimen shift from dual to monotherapy is recommended in case of multiple irAEs. We are aware that our study has some limitations since only one patient experienced a high grade ir-meningitis. A careful analysis of the risk/benefit ratio should be done on a case-by-case basis.

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