Case Series

Melanoma Management

Immune checkpoint inhibitors in the treatment of advanced mucosal melanoma

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Immunotherapy with immune checkpoint inhibitors is the standard of care in the treatment of advanced melanoma. Treatment outcome of these agents is less defined for the rare subtype of mucosal melanoma. In this single-institutional case series, the objective response rate was low at 11.8%, but durable response was seen, including a complete response to first-line ipilimumab and to second-line pembrolizumab. Survival remained poor; at the median follow-up of 10.1 months, the median progression-free survival and overall survival were 3.1 and 8.8 months respectively. Nevertheless, among the few responders, survival of up to 56+ months was observed. Other treatment strategies need to be explored to improve treatment outcome for this rare subtype.

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Practice points

- Mucosal melanoma is a rare subtype of melanoma for which the treatment outcome with immune checkpoint inhibitors (ICIs) is less clear in comparison to that for cutaneous melanoma.
- Case series and pooled analysis have been reported, demonstrating efficacy of ICIs in this subtype of melanoma, with an objective response rate ranging from 6.7 to 33.3% with single agent and 37.1% with dual-agent combination.
- Although the objective response rate may be low, durable response has been observed with ICIs, either in the first-line or second-line setting.
- Sequential use of ICIs is an appropriate treatment strategy: durable response to pembrolizumab in the second-line setting, despite a lack of response to first-line ipilimumab, may be achieved.
- Combination of immune oncology agents have demonstrated significantly improved response rate and survival in advanced cutaneous melanoma and is to be considered as the standard of care for patients with advanced mucosal melanoma.
- Other future treatment strategies becoming available for patients with advanced cutaneous melanoma should be offered to patients with advanced mucosal melanoma.

Immune checkpoint inhibitor (ICI) therapy is the standard of care in the systemic treatment of advanced or metastatic melanoma; these monoclonal antibodies target different receptors along the tumor-immunity cycle, including CTLA-4 with ipilimumab and tremelimumab, PD1 with nivolumab and pembrolizumab, and PD-L1 with durvalumab and atezolizumab. The anti-CTLA-4 achieved a response rate of approximately 10% in melanoma and was the first agent to demonstrate an improved overall survival (OS) of 10–12 months [1,2]. Subsequent trials had confirmed the superiority of anti-PD1 over ipilimumab in achieving a better response rate and OS [3,4]. Experience with anti-PD-L1 has so far been limited to Phase I trials only.

Durable response with long-term survival has been demonstrated with ICI therapy. In previously untreated patients, the 3-year survival rate with ipilimumab was reported to be 26% in a pooled analysis [5], and as high as 31.2% in a Phase III trial [6]. More promising data were reported with pembrolizumab and nivolumab, demonstrating, respectively, a 3-year survival rate of 40% [7] and a 2-year survival rate of 59% [4]. Combination ICI strategies are likely to improve the durability of treatment response and further improve OS with the combination of nivolumab and ipilimumab already demonstrating a superior progression-free survival (PFS) over ipilimumab alone [8].

Future Medicine

Table 1. Patient overview.

Pt#	Age (years)/sex	Primary site[†]	Mutation status[‡]	M1c disease	ECOG PS	Prior tx[§]	ICI agent	Best response	PFS (months)	Tx post PD	OS (months)
1	83/F	1	0	Yes	1	1	Ipilimumab	PD	3.6	Another ICI	49.3
2	58/F	3	0	Yes	1	1	Ipilimumab	PD	3.1	Another ICI	57.6+
3	40/F	2	1	Yes	1	0	Ipilimumab	PD	4.1	Chemotherapy	12.5
4	49/F	3	0	Yes	0	0	Ipilimumab	PD	3.9	Clinical trial	18.7
5	45/F	1	0	Yes	1	0	Nivolumab	PD	2.5	BSC	2.8
6	81/F	1	0	Yes	1	1	Ipilimumab	PD	0.8	BSC	0.8
7	61/M	1	2	Yes	1	1	Ipilimumab	PD	0.9	BSC	1.3
8	68/F	3	0	Yes	1	1	Ipilimumab	PD	1.1	BSC	1.1
9	64/M	2	0	Yes	1	0	Ipilimumab	PD	3.0	Another ICI	8.8
10	39/M	2	0	No	1	1	Ipilimumab	PR	5.0	Another ICI	10.1
11	73/F	3	3	No	0	0	Ipilimumab	CR	NR, 21.2+	N/A	NR, 21.2+
12	38/F	2	0	Yes	1	0	Ipilimumab	N/A[¶]	N/A	Another ICI	10.3
13	59/F	3	0	Yes	0	2	Ipilimumab	PD	2.8	Another ICI	NR, 18.6+
14	65/F	3	2	No	0	3	Pembrolizumab	SD	5.8	Chemotherapy	NR, 11.3+
15	41/F	2	1	Yes	1	0	Pembrolizumab	PD	5.1	BSC	6.2
16	67/F	1	0	No	0	0	Pembrolizumab	SD	NR, 1.4+	N/A	NR, 1.4+
17	71/F	2	0	Yes	1	0	Pembrolizumab	SD	NR, 1.0+	N/A	NR, 1.0+

[†]1: head and neck; 2: anorectal/gastrointestinal; 3: vulvovaginal.
[‡]0: none detected; 1: unknown; 2: *NRAS*; 3: *cKIT*.
[§]0: none; 1: chemotherapy; 2: liver-directed therapy; 3: investigational agent on clinical trial.
[¶]Planned switch to another ICI agent.
BSC: Best supportive care; CR: Complete response; ECOG PS: European Cooperative Oncology Group performance status; F: Female; ICI: Immune checkpoint inhibitor; M: Male; N/A: Not available; NR: Not reached; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; Pt#: Patient number; SD: Stable disease; Tx: Treatment.

However, the role of ICI in treating rare subtypes of melanoma remains less defined. Mucosal melanoma is an aggressive subtype, which, although not excluded from randomized clinical trials with ICI accruing patients with advanced melanoma, has been under-represented due to its rarity. Without having been separately reported, the efficacy of ICI therapy in mucosal melanoma is unclear. A retrospective, single-institutional study was therefore conducted to examine the use of ICI therapy in patients with advanced mucosal melanoma to better understand the benefit of ICI for this patient population.

Case series

Over the 3-year period between 1 January 2014 and 31 December 2016, a total of 21 patients diagnosed with advanced mucosal melanoma were reviewed to discuss systemic therapy and 17 proceeded to receive at least one dose of ICI therapy, including ipilimumab (n = 12), pembrolizumab (n = 4) and nivolumab (n = 1). Two patients received ipilimumab on the clinical trials CheckMate-067 (NCT01844505) and KEYNOTE-006 (NCT01866319), and another received nivolumab on the CheckMate-067 trial; all the other patients received either ipilimumab or pembrolizumab outside the setting of a clinical trial. Six patients had prior systemic therapy with chemotherapy, including dacarbazine (n = 2) and combination carboplatin and paclitaxel (n = 6); two patients had two lines of chemotherapy. A total of 14 patients had M1c disease, staged according to the American Joint Committee on Cancer classification for cutaneous melanoma; nine patients had elevated lactate dehydrogenase (LDH) at the time of initiating ICI therapy.

Most patients (n = 15) had tumor genomic profiling done: a mutation in *KIT* or *NRAS* was found in three patients. A 74-year-old female with vulvovaginal mucosal melanoma had two *KIT* alterations: *Tyr646Cys* and *Asp820Val*, neither of which was previously reported in melanoma and was of unknown clinical significance. A 65-year-old female with vulvovaginal primary had an *NRAS Gln61Lys* mutation. Another 60-year-old male with a primary arising from the upper alveolar ridge had an *NRAS Gly13Asp* mutation. A total of 12 patients had no mutations detected. None had known tumoral PD-L1 status.

All relevant clinical data including baseline patient and tumor characteristics as well as a treatment summary are presented in Table 1. Baseline patient characteristics are summarized in Table 2.

Details of treatment outcome are summarized in Table 3. Best treatment response was assessed according to the

Table 2. Baseline clinical characteristics.

Characteristics	Number
Age at the time of treatment	
Median (range)	61 (39–83) years
Age category (years)	
<65	10
65–75	5
>75	2
Sex	
Male	3
Female	14 (82.3%)
ECOG performance status	
0	5
1	12
Site of primary	
Head and neck	5
Vulvovaginal	6
Anorectal/GI	6
M stage	
M0	2
M1a/M1b	1
M1c	14
LDH	
≤ULN	8
>1–2 × ULN	7
>2 × ULN	2
Brain metastases	
Yes	1
No	16
Liver metastases	
Yes	7
No	10
Mutations	
BRAF	0
KIT	1
NRAS	2
Wild-type	12
Unknown	2
Prior systemic therapy	
Yes	6
No	11

ECOG: European Cooperative Oncology Group; GI: Gastrointestinal; LDH: Lactate dehydrogenase; ULN: Upper limit of normal.

Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and one complete response (CR), one partial response (PR) and three stable diseases were identified. The progress of each patient was followed until the data cut-off date of 1 March 2017 to determine the PFS, as calculated from the date of the first dose of ICI to the date of first documented progression as per RECIST, change in therapy or the last clinical follow-up, and OS, as calculated from the date of the first dose of ICI to the date of death from any cause or the last clinical follow-up.

In the 11 patients who received ipilimumab, three patients ceased treatment after one or two doses due to rapid clinical deterioration and died shortly afterwards. Another two patients ceased treatment due to immune-related toxicities: one had nephritis after three cycles, and subsequently the disease progressed within 3 weeks thereafter, and the other had colitis after two cycles, but had a sustained PR over the following 5 months. Six patients

Table 3. Treatment outcome.	
Number evaluable	17
Best response	
Complete response	1
Partial response	1
Stable disease	3
Progressive disease	12
Objective response rate (%)	11.8
– to ipilimumab (n = 12)	18.2
– to anti-PD1 (n = 5)	0
Disease control rate (%)	29.4
– to ipilimumab (n = 12)	18.2
– to anti-PD1 (n = 5)	50
PFS, median (range), months	3.1 (0.9–5.8)
– to ipilimumab (n = 12)	3.0 (0.8–21.0+)
– to anti-PD1 (n = 5)	4.2 (0.9–5.8)
OS, median (range), months	8.8 (6.2–49.3)

PFS: Progression-free survival; OS: Overall survival.

Table 4. Outcomes of ipilimumab-treated patients who received pembrolizumab.

Pt#	Best response to ipilimumab	Time (days) between PD and pembrolizumab	Best response to pembrolizumab	Total cycles received	PFS (months)[†]	OS (months)[†]
1	PD	29	PR	41, ceased due to PD	36.9	44.7
2	PD	187[‡]	CR	33, ceased due to CR/AE	NR, 47.4+	NR, 47.4+
9	PD	15	PD	4, ceased due to PD	2.3	5.3
10	PR	34	PD	2, ceased due to PD	1.8	3.9
12	Not assessed	21 (planned switch)	PD	3	3.2	9.6
13	PD	39	SD	20+, ongoing	NR, 13.5+	NR, 13.5+

[†]From time of initiating pembrolizumab.
[‡]This patient received chemotherapy with four cycles of carboplatin/paclitaxel and had a sustained PR of 5 months.
AE: Adverse event; CR: Complete response; NR: Not reached; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; Pt#: Patient number; SD: Stable disease.

completed four doses of ipilimumab: one patient had a durable CR, with PFS not reached (NR) at the time of data cut-off, more than 21 months after initiating ipilimumab, and the other five patients had radiological PD confirmed within 3–4 months after treatment was initiated. The median PFS (mPFS) for the ipilimumab-treated patients was 3.0 months (range of 0.8 month to NR [more than 21 months]). In the five patients who received pembrolizumab, a median of three doses was administered; two patients were receiving ongoing treatment at the time of data cut-off. For the other three patients, one ceased due to immune-related rash after four doses and two ceased due to PD after three and seven doses, respectively. The mPFS for the pembrolizumab-treated patients was 5.1 months (range of 0.9–5.8 months). One patient who received nivolumab had a total of eight cycles but PD was confirmed on the first restaging imaging; the PFS was 2.5 months.

Upon confirmed PD after treatment with ipilimumab, five patients received second-line pembrolizumab. Two patients were enrolled in the Phase I KEYNOTE-001 clinical trial (NCT01295827) and had a remarkable response: one received a total of 41 cycles with a PR sustained for 36.9 months, and another had a total of 33 cycles, ceased due to accumulated immune-related adverse events but at the time had attained a CR for 47.4 months, ongoing at the time of data cut-off. Three patients received pembrolizumab via a compassionate access scheme: one had stable disease sustained for 13 months and ongoing at time of data cut-off and the other two had PD after two and four doses of treatment before a rapid clinical deterioration and died within 3 months after treatment was ceased. One patient did not have a response assessment after one single dose of ipilimumab because of a pre-planned switch to pembrolizumab, and received a total of three doses of pembrolizumab prior to a confirmed PD. The treatment outcome of these six patients is summarized in Table 4.

Table 5. Summary of literature review reporting treatment outcome of immune checkpoint inhibitor in mucosal melanoma.

Study	Agent	n	ORR (%)	CR (%)	DCR (%)	mPFS (month)	mOS (month)	Ref.
Postow *et al.*	Ipilimumab	30	6.7	0.3 (n = 1)	26.7	N/A	6.4	[16]
Alexander *et al.*	Ipilimumab	8	N/A	N/A	N/A	2.7	5.8	[17]
Del vecchio *et al.*	Ipilimumab	71	11.3	0.01 (n = 1)	35.2	4.3	6.4	[18]
Zimmer *et al.*	Ipilimumab	6	17	0	50	N/A	9.6	[19]
Shoushtari *et al.*	Anti-PD1†	35	22.9	0	42.9	3.9	12.4	[15]
D'angelo *et al.*	Nivolumab	86	23.3	5.8 (n = 5)	45.3	3.0	N/A	[14]
	Ipilimumab	36	8.3	0	16.7	2.7	N/A	
	Ipilimumab + nivolumab	35	37.1	2.9 (n = 1)	57.1	5.9	N/A	
Takahashi *et al.*	Nivolumab	27	33.3	7.4 (n = 2)	40.7	N/A	N/A	[20]
Butler *et al.*	Pembrolizumab	84	19	N/A	31	2.8	11.3	[13]
Schaefer *et al.*	Ipilimumab	8	12.5	0	25	N/A	N/A	[21]
	Anti-PD1†	7	28.6	0	28.6	N/A	N/A	

†Either nivolumab or pembrolizumab.
CR: Complete response; DCR: Disease control rate; mOS: Median overall survival; mPFS: Median progression-free survival; n: Number; N/A: Not available; ORR: Objective response rate.

After ICI therapy, five patients continued to receive further systemic therapy, including chemotherapy and investigational agent in a Phase I clinical trial. In all patients, the median follow-up, to the point of data cut-off, was 10.1 months (range of 0.8–56.6 months). Overall survival was NR for six patients with one patient lost to follow-up, and ten patients died; the median OS (mOS) was 8.8 months (range of 6.2–49.3 months).

Discussion

Primary mucosal melanoma is rare, aggressive and typically diagnosed late, on average 1–2 decades later than cutaneous melanoma [9]. There is a female predominance due to the development of disease in the female genital tract [10]. Although the incidence of cutaneous melanoma has been increasing over time, the incidence of mucosal melanoma has remained relatively stable, accounting for approximately 1% of all melanoma [11,12].

Several case series and, more recently, pooled analyses have reported the treatment outcome with ICI in mucosal melanoma; these are summarized in Table 5. Of note, the response rate to pembrolizumab from a pooled analysis among 84 patients from three clinical trials, KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006, was 19%, and a durable response with a median of 27.6 months was demonstrated in the responders (n = 16) [13]. A pooled analysis of nivolumab in 86 patients from five clinical trials, CA209-003, CA209-038, CheckMate-066, CheckMate-037 and CheckMate-067, identified an objective response rate of 23.3% with the median duration of response NR at the time of data cut-off [14]. Moreover, a multi-institutional retrospective study of 35 patients treated with either pembrolizumab or nivolumab, mostly (53%) outside the clinical trial setting, found a response rate of 23% with a median duration of response of 12.9 months; mPFS and mOS were 3.9 and 12.4 months, respectively [15].

This single-institutional experience appears to contrast that reported in the literature, in that upfront anti-PD1 did not achieve any objective response, and, conversely, response to upfront ipilimumab was better than any previously reported. The difference in response rate seen between this report and the others in the literature is multifactorial and highlights the intrinsic difficulties in comparing data between different case series. There are potentially multiple confounding factors, and predictive factors for treatment response with ICI have remained elusive, although progress has been made, suggesting that pre-existing mutational defects may lead to primary resistance to ipilimumab [22], and an absence of adaptive immune response in the tumor microenvironment may result in acquired resistance to pembrolizumab [23]. Irrespective to the underlying mechanism, it is clear that the clinical benefit of ICI is limited to a small subset of patients only, given the modest median survival seen across all reports. Limitations due to the retrospective nature of, and the small number included in, this case series compromise the generalizability of the findings. Nevertheless, it is demonstrated that a durable response is achievable, notably in the second-line setting with pembrolizumab following disease progression after ipilimumab.

Pembrolizumab is considered the standard of care in patients with advanced cutaneous melanoma that progressed on ipilimumab. The KEYNOTE-002 trial demonstrated an mPFS of 5.4 months [24] and an mOS of 13.4 months [25]. The finding of this study is supportive of the use of pembrolizumab in ipilimumab-pretreated patients with mucosal melanoma: four patients with disease progression after ipilimumab achieved durable disease control, including one CR sustained at the time of data cut-off for more than 47 months since commencing pembrolizumab. Recent data suggest that the sequential treatment with nivolumab followed by ipilimumab appeared to improve survival comparing to that of the reverse sequence [26], and a sequential ICI strategy in treating mucosal melanoma should be considered an appropriate option as well.

As selected patients with advanced mucosal melanoma can benefit from ICI, further treatment strategies with immunotherapy should be investigated. It has become clear that combining ipilimumab with an anti-PD1, followed by anti-PD1 monotherapy maintenance, is a feasible first-line treatment option, improving objective response rate and survival comparing to ipilimumab alone, although at the cost of substantially increased toxicity [8,27–28]. Moreover, combining ipilimumab and pembrolizumab after sequential ipilimumab and pembrolizumab failure had demonstrated further benefit with acceptable toxicity profile in a small study of nine patients [29]. Evidence related to the strategy of safely administrating combination of ipilimumab and nivolumab from the CheckMate-511 trial (NCT02714218) is eagerly awaited. Moreover, the Phase II trial recently opened to accrual, the IND.228 (NCT02879162), specifically investigates the role of combination immunotherapy in mucosal melanoma, with tremelimumab, an anti-CTLA4, and durvalumab, an anti-PD-L1; result is estimated to become available in 2020.

Conclusion

Extrapolating evidence derived from large clinical trials with ICI to treat patients with advanced mucosal melanoma will continue as this rare melanoma subtype will remain under-represented in those trials. Treatment with ICI is nevertheless effective and can, albeit at a lower response rate, induce a durable response. Except for patients who attain an exceptional response, survival remains poor. Sequential or combination ICI needs to be explored as the potential standard of care to improve treatment outcome, and further research in biomarkers may assist in patient selection for ICI therapy.

Future perspective

Strategies being investigated to overcome immunotherapy resistance, for example, the combination of different checkpoint inhibitors, may be applicable in the treatment of metastatic mucosal melanoma, and the results of clinical trials specifically designed for mucosal melanoma patients are eagerly awaited.

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•• **The first report of a pooled analysis outlining the treatment outcome to pembrolizumab for patients in the clinical trial setting.**

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