Brief Report

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Pembrolizumab for the treatment of uveal melanoma: A case series

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Abstract

Uveal melanoma is a rare disease. Up to 50% of the patients will develop metastases for which the treatment options are limited. No randomized controlled data for the treatment of uveal melanoma patients are available. In this study we describe the clinical course of nine uveal melanoma patients included in the pembrolizumab expanded access program (EAP) in Belgium. Nine uveal melanoma patients were treated in the EAP with 2mg/kg pembrolizumab every 3 weeks. Patients received pembrolizumab as first or second-line treatment. Baseline characteristics and tumor responses were prospectively collected. During a median follow-up of 40 weeks, the estimated median PFS was 18 weeks (95% CI 0.7–35) and median OS was 46 weeks (95% CI 33–59%). Four patients had stable disease (SD) for more than 20 weeks (PFS of 21, 22, and 27 weeks respectively) and 1 patient presented with SD for 119 weeks. No objective responses according to irRC were observed. One grade 3 hepatitis occurred which was reversible with the administration of high doses oral corticosteroids. Even though treatment with pembrolizumab is well tolerated, clinical benefit is disappointing. Nevertheless long-term diseases control can be achieved in selected cases

Keywords

Uveal melanoma, anti-PD-1 treatment

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Introduction

Uveal melanoma is a rare malignancy, occurring in 5.3 to 10.9 cases per million inhabitants per year. It arises from the melanocytes of the uveal tract of the eye (iris, ciliary body and choroid). When found in a non-metastasized stage, local treatment is aggressive and is guided by the tumor size, localization, vision impairment and extra-ocular extension. Despite an aggressive local treatment, 50% of the patients will develop metastasis. The prognosis for stage IV uveal melanoma is grim with an overall survival (OS) of 6 to 10 months and a 1-year survival rate of 15%.[1] These survival rates have not changed in the last decades despite different chemotherapeutical regimens, the use of radiotherapy and the introduction of immunotherapy. A review from Buder et al. in 2013 on all clinical trials in metastatic uveal melanoma, demonstrated low overall therapy responses. An

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objective response (partial response (PR) or complete response (CR)) with current treatments was seen in only 39 out of 841 treated patients. The progression free survival (PFS) ranged from 1.8 to 7.2 months and the OS from 5.0 to 19 months.[2]

In cutaneous melanoma, the therapeutic landscape changed dramatically with the discovery of targeted therapy and immunotherapy. Unfortunately, cutaneous melanoma is different from uveal melanoma. As an example, uveal melanoma cells do not harbor BRAF mutations but 80% of the uveal melanoma's harbor a mutations in GNAQ or GNA11 (GNAQ11).[3] Like BRAF, GNAQ/11 is a part of the Mitogen-activated protein kinase (MAPK) pathway. Unfortunately, where BRAF inhibitors[4] have a high efficacy in cutaneous melanoma, the selective inhibition of GNAQ/11 with selumetinib[5] leads to a modest improvement of PFS and no improvement of OS. This is probably because GNAQ/11 is downstream in the MAPK signaling pathways leading to more intrinsic resistance.

Unfortunately, data about immunotherapy in uveal melanoma is scares. Uveal melanoma patients are excluded from most clinical trials so most data is derived from expanded access programs (EAPs). Ipilimumab, a CTLA-4 inhibitor, appears to improve OS but not PFS and the objective response rate is low. Maio et al. indicated a 1-year survival rate of 31%.[6] In the Phase II DeCOG-study evaluating the responses to ipilimumab in pre-treated and treatment naïve patients,[7] no objective tumor responses were seen in 53 treated patients (45 pre- treated and 8 first line treatment). The median OS was 6.8 months (95% CI 3.7–8.1). They concluded that even though ipilimumab was well tolerated, clinical activity of ipilimumab in uveal melanoma was minimal.

In 2016, data about the use of pembrolizumab in uveal melanoma became available. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, which will lead to T-cell–mediated immune responses against tumor cells. Data from three small cohorts are available; Karydis et al. demonstrated a PR in 2 out of 25 patients and Agazi et al. demonstrated a PR in 2 out of 56 patients. In both cohorts, no CRs were achieved. PFS was short, respectively, at 3 and 2.6 months. This is in contrast to the data shown by kottschade et al. They demonstrated a CR in 1 of ten treated patients and a PR in 2 out of 10 treated uveal melanoma patients.[8–10]

In this case series we describe the responses of nine uveal melanoma patients treated in the EAP of pembrolizumab in Belgium

Materials and methods

Patients

The pembrolizumab EAP program opened in Belgium on September 1, 2014. Until February 14, 2016, only patients with unresectable stage III/IV melanoma (uveal, mucosal and skin) failing standard of care were included in the EAP. After February 14, 2016, the EAP was expanded to first line treatment. The study protocol was approved by the medical ethical committee of the university hospital of Brussels (UZB-BN-2014-001) and registered on clinical trials.gov (NCT02673970). Written informed consent was obtained from the patients for their anonymized information to be published in this article. In April 2016, the EAP was closed due to approved reimbursement in Belgium.

All uveal melanoma patients treated in the EAP were included in this case series.

Study design

This single center, prospective trial was conducted at the university hospital of Brussels. Tumor responses were evaluated using the immune–related response criteria in solid tumors (irRC).

Pembrolizumab at a dose of 2 mg/kg was administered every 3 weeks until disease progression or severe drug related toxicity or patient/physician guided decision to stop therapy.

Statistical methods

All statistical analyses were performed using SPSS Statistics 24.0 software. OS and PFS were estimated from the first dose of pembrolizumab to the time of last follow up, death, or disease progression.

Results

Patients

In total, 141 melanoma patients were treated with pembrolizumab in the EAP, of which nine uveal melanoma patients. Baseline patient characteristics are provided in Table 1. All uveal melanoma patient had staged IV disease. Eight (89%) patients had liver metastases and 7 (78%) had more than three sites affected by metastases. Only 2 (22%) patients had a LDH $>$ 1.5 ULN (22%) and no patients had a LDH $>$ 2*x* ULN.

The average number of pembrolizumab treatments was 10 doses (range 5–32). About 8 (88%) patients discontinued treatment due to disease progression. At the time of analysis, only 1 (11%) patient was continuing pembrolizumab. About 6 (67%) patients died due to disease progression.

About 2 (22%) patients received pembrolizumab as a first line treatment. About 7 (78%) patients received ipilimumab treatment prior to pembrolizumab (2 patients: 2 cycles, 2 patients: 3 cycles, and 3 patients: 4 cycles). Best objective response (BOR) on ipilimumab was a stable diseases (SD) in four patients and progressive diseases in 3 patients. The average time between the last ipilimumab

Table 1. Baseline demographics and clinical characteristics.

	No	%
Median age	61	40–84
Gender		
Men	2	22
Woman	7	78
Stage IV disease	9	100
LDH		
LDH normal	3	33
LDH > ULN	4	44
LDH > 1.5 ULN	2	22
LDH > 2ULN	0	0
CRP		
CRP normal	6	67
CRP > ULN	3	33
CRP > 5ULN	1	11
CRP > 10ULN	0	0
ALC		
>2000	2	22
<2000	3	33
<1500	2	22
<1000	2	22
ANC > 7500	0	0
Eosino > 100 < 103	9	100
Metastatic sites		
Liver	8	89
Lung	3	33
Bone	5	56
Subcutaneous	4	44
Brain	0	0
>3 sites	7	78
ECOG performance status		
0	5	55
1	2	22
2	2	22
Prior ipilimumab	7	78
No of prior therapy's including ipilimumab		
0	2	22
1	1	11
2	6	67
⩾3	0	

LDH: lactate dehydrogenase; CRP: C-reactive protein; ALC: absolute leukocyte count; ANC: absolute neutrophil count; Eosino: absolute eosinophil count; ECOG: Eastern Cooperative Oncology Group Performance; No: number

Table 2. Best objective response rate.

	No.	%		
irCR	0	0	ORR: 0%	DCR: 56%
irPR	0	0		
irSD	5	56		
irPD	4	44		

ir: immune-related response criteria; CR: complete remission; PR: partial response; SD: stable disease; PD: progressive disease; OR: objective response rate; DCR: disease control rate; No: number.

treatment and first pembrolizumab was 14 weeks (range 0.5–58 weeks).

Efficacy and overall survival

No patient obtained an objective response according to irRC, 5 (56%) patients had stable disease (SD) for more than 20 weeks (PFS of 21, 22, and 27 weeks and ongoing) leading to an overall disease control rate of 56% (Table 2, Figure 1). Five (56%) patients maintained a SD. One (11%) patient had a SD for more than 2 year (119 weeks). This patient was still on treatment at the time of analysis. Four (44%) patients did not benefit pembrolizumab treatment. After a median follow up of 40 weeks the estimated PFS was 18 weeks (95% CI 0.7–35) and the median OS was 46 weeks (95% CI 33–59%). The estimated 1-year PFS and OS rates was 22% and 11% respectively. For the 2 (22%) patients treated in a first line setting, PFS was 12 and 27 weeks and OS was 25 and 37 weeks, respectively. The groups were too small to establish predictive or prognostic factors.

Safety

A total of 8 (88%) patients developed an adverse event. The most common adverse event was fatigue, occurring in 6 (67%) patients (all grade ⩽2). One patient developed a hepatitis grade 3 requiring high doses of oral corticosteroids. This patient also developed a thyroiditis with an evolution from hyperthyroidism to hypothyroidism requiring a beta-blocker at the time of hyperthyroidism and substitution of thyroid hormones afterwards. All adverse events are listed in Supplemental Tables 3 and 4.

Discussion

PD-1 and PD-L1 inhibitors changed the therapeutic landscape of cutaneous melanoma. However, uveal melanoma patients were excluded from the clinical trials. Karydis et al and Algazi et al. evaluated the responses in uveal melanoma patients and the results were disappointing with an objective response of less than 8%.[8–10] Although our case series consists of small numbers, it does support their conclusion. Only one patient in our cohort obtained a true durable stable disease (>2 years) and no objective response were observed.

The treatment of uveal melanoma remains a challenge. Being a rare disease, experience in the treatment of uveal melanoma patients is limited and interest from pharmaceutical companies remains low. Additional clinical trials with PD-1 monotherapy and combination therapy (with ipilimumab or other cytotoxic agents) are still ongoing.

Maybe the key to identifying a successful treatment in uveal melanoma is to understand its biology. Oliva et al[1]

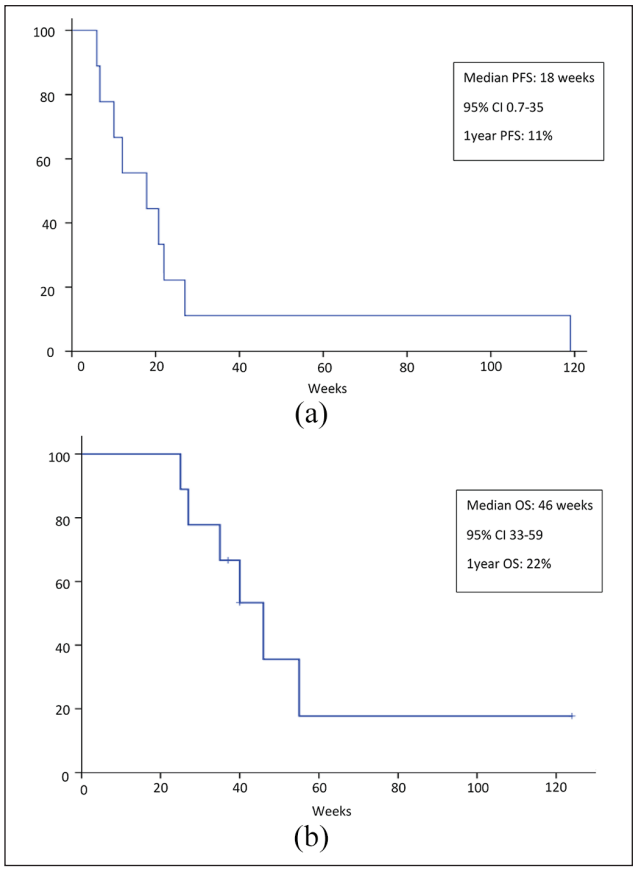

Figure 1. Kaplan Meier survival curves: (a) progression free survival and (b) overall survival.

postulated that uveal melanoma cells use the immunosuppressive environment, created by the eye, to escape the immune system. They evade immune surveillance through mechanisms that involve both the innate and adoptive responses. One of the key factors of this immune privileged environment is indoleamine 2, 3-deoxygenase (IDO) in corneal cells. IDO is an inducible enzyme, which acts as a catalyst, triggering the degradation of tryptophan. The depletion of tryptophan will consequently lead to the inhibition of T-cells and dendritic cells.[11–13] PD-L1 also seems to play a role and is constitutively expressed in 50% of the primary uveal melanoma but only in 20% of uveal melanoma metastases. Literature suggests that a high T-cell infiltration in uveal melanoma is frequent. However, in contrary to other solid tumors, the infiltration with T-cells is correlated with a worse prognosis and higher risk of metastasis.[14–17] These data suggest a possible role for immunotherapy in the treatment of uveal melanoma. Therefore, if T cells (both T-helper and cytotoxic T-cells) are present in uveal melanoma and one of the immune escape mechanism for uveal melanoma leading to T-cell inhibition is expression of IDO. The combination of a checkpoint inhibitor and IDO-inhibitor could potentially lead to a better t-cell-mediated immune response against uveal melanoma.

Conclusion

Even though PD-1 treatment is safe in uveal melanoma patients with adverse events comparable to other tumor types, objective responses are rare. Although the clinical benefit from PD-1 inhibitors monotherapy is low in uveal melanoma patients, some selected cases do show long-term disease control. At present, the inclusion of uveal melanoma patients in ongoing clinical trials remains the best therapeutic option.

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Authors' contributions

JLYJ: writing manuscript, recruiting patients, and data analysis. TS: review of manuscript and recruiting patients; BN: review of manuscript and recruiting patients.

Declaration of conflicting interests

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Informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Ethical approval

The study protocol was approved by the medical ethical committee of the university hospital of Brussels (UZB-BN-2014-001) and registered on clinical trials.gov (NCT02673970).

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Supplemental material

Supplemental material for this article is available online.

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