Clinical Oncology: Case Reports

CASE REPORT

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A Case Report of a Patient with Metastatic Uveal Melanoma who Experienced a Complete Response to Treatment with the NIVO3+IPI1 Regimen

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Abstract

Background: Uveal melanoma is a rare malignancy and in the advanced setting there is no effective treatment. Therefore, combined checkpoint blockade with nivolumab 1 mg/kg and ipilimumab 3 mg/kg (NIVO1+IPI3) is frequently used despite low response rates and high immune-related toxicity. There are hardly any reports on the less toxic combination of nivolumab 3 mg/kg and ipilimumab 1 mg/kg schedule (NIVO3+IPI1) in these patients.

Case presentation: We used the NIVO3+IPI1 schedule to treat a 56-year-old male suffering from metastatic uveal melanoma. The patient experienced a clear and long-lasting benefit from the treatment. An improvement of his general condition was observed almost immediately after treatment start. A complete metabolic response which is still ongoing was achieved over a year ago and a complete response according to RECIST 1.1 criteria was evident at the most recent CT scan.

Conclusions: To our knowledge, this is the first described case of complete response to NIVO3+IPI1combined immunotherapy in a patient with metastatic uveal melanoma.

Keywords

Metastatic uveal melanoma; Complete response; NIVO3+IPI1 regimen

Background

Uveal Melanoma (UM) is a rare malignancy arising from the eye, distinct from cutaneous Malignant Melanoma (MM) and other melanoma subtypes. Although it is the most common malignant intraocular tumor in adults the incidence of UM is much lower than that of MM [1]. Uveal melanoma is characterized by a low mutational burden and does not harbor mutations in BRAF or NRAS present in MM [2]. More than 50% of all cases will eventually develop metastases due to hematogenous spread during the course of the disease. The liver is the predominant metastatic site. The prognosis remains very poor when distant metastases have occurred. One third of the patients diagnosed with primary UM will die of systemic metastases within five years of diagnosis, and approximately 50% are deceased within 15 years [3-5].

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Despite the treatment innovations achieved in MM over the past few years, every new treatment has failed to demonstrate clear benefits in patients with metastatic UM (mUM) [6,7]. However, promising results were recently presented in patients treated with the bispecific antibody tebentafusp [8]. Studies on combined checkpoint blockade with ipilimumab 3 mg/kg and nivolumab 1 mg/kg (NIVO1+IPI3) in patients with metastatic MM indicate response rates and survival outcomes superior to monotherapy with PD-1 inhibitor but at the cost of higher immune-related toxicity [9]. One study shows equal benefit from the less toxic NIVO3+IPI1 schedule in these patients [10]. However, the significance of checkpoint blockade in patients with mUM still remains unclear and especially for the NIVO3+IPI1 schedule [11-13].

Here, we present a case of a patient with mUM who was treated with ipilimumab 3 mg/kg body weight and nivolumab 1 mg/kg body weight (NIVO3+IPI1) in which Complete Response (CR) was achieved. To our knowledge, there is no previously described case of CR to NIVO3+IPI1 in metastatic ocular melanoma.

Case Presentation

The patient, a 56-year old Caucasian man, noticed flashes and flickers in the right eye in 2001. Due to progression of these symptoms an investigation was initiated. Eventually he was diagnosed with UM of the right eye and enucleation was carried out in March, 2003. In line with national recommendations the patient underwent ultrasound of the liver every 6 months without signs of metastatic disease. The last scheduled control took place at the Oncology Department, Uppsala University Hospital in August, 2009.

Due to pain in the left side of the abdomen a Computed Tomography (CT) was performed on the 23th of March, 2019. The CT showed left ureteral concretion and multiple suspected liver metastases of varying size. The patient was referred to the Oncology Department on the 2th of April, 2019 for further investigation. An ultrasound-guided liver biopsy was performed on the 4th April and the patient underwent an 18-FDG-PET/CT (PET/CT) two days later. The PET/CT showed, except from multiple liver metastases, two bone metastases in Th6 and Th7 respectively (Figures 1a and 1b). The pathology report confirmed that the patient was suffering from mUM. The combination of nivolumab/ipilimumab was not recommended for treatment of metastatic uveal melanoma at that time in Sweden. The laboratory samples showed slightly elevated levels of transaminases as well as of Lactate Dehydrogenase (LDH). The clinical examination revealed a quite enlarged liver. Treatment with temozolomide (200 mg/m^2 for 5 days every 4th week) and denosumab (120 mg once every 4th week) due to the bone metastases was initiated on 17th April, 2019. Rapid deterioration of the patient's general condition with severe pain below right arcus as well as increasing levels of transaminases (2.5 × ULN, upper limit of normal), LDH (3 × ULN) and Alkaline Phosphatase (ALP) was noted already after one treatment course.

Since May 2019 combination immunotherapy for mUM may be considered according to the national Swedish guidelines. The patient received his first treatment with nivolumab 3 mg/kg+ipilimumab 1 mg/kg (NIVO3+IPI1) on May 15th, 2019. He received four such cycles before the initiation of single nivolumab 480 mg every 4 weeks (Q4W)

on 9th September, 2019. Due to the COVID-19 pandemic the patient received pembrolizumab 400 mg Q6W instead of nivolumab from the 27th of April 2020 in order to reduce the number of visits to our department.

In July 2019, both the laboratory values and the size of the liver were normalized and remained normal at the latest follow-up in February 2021. The patient´s general condition was considerably improved as well. The first PET/CT scan evaluation was performed in August 2019, after four cycles of combined immunotherapy. It showed partial metabolic response (PMR) in liver metastases, the bone metastases had no uptake but there were a few new mediastinal lymph nodes with new uptake, suspicious of inflammatory reaction.

The patient was referred to the pneumology department in order to undergo further investigation. He continued to receive nivolumab and denosumab and a new PET/CT-scan was performed in October that showed Complete Metabolic Response (CMR) and unchanged mediastinal lymphadenopathy. A biopsy of those lymph nodes in November, 2019 showed mild sarcoidosis. A new PET/CT-scan in January 2020 showed CMR-although SD according to RECIST 1.1 and no mediastinal lymphadenopathy (Figures 1c and 1d). Thereafter, the

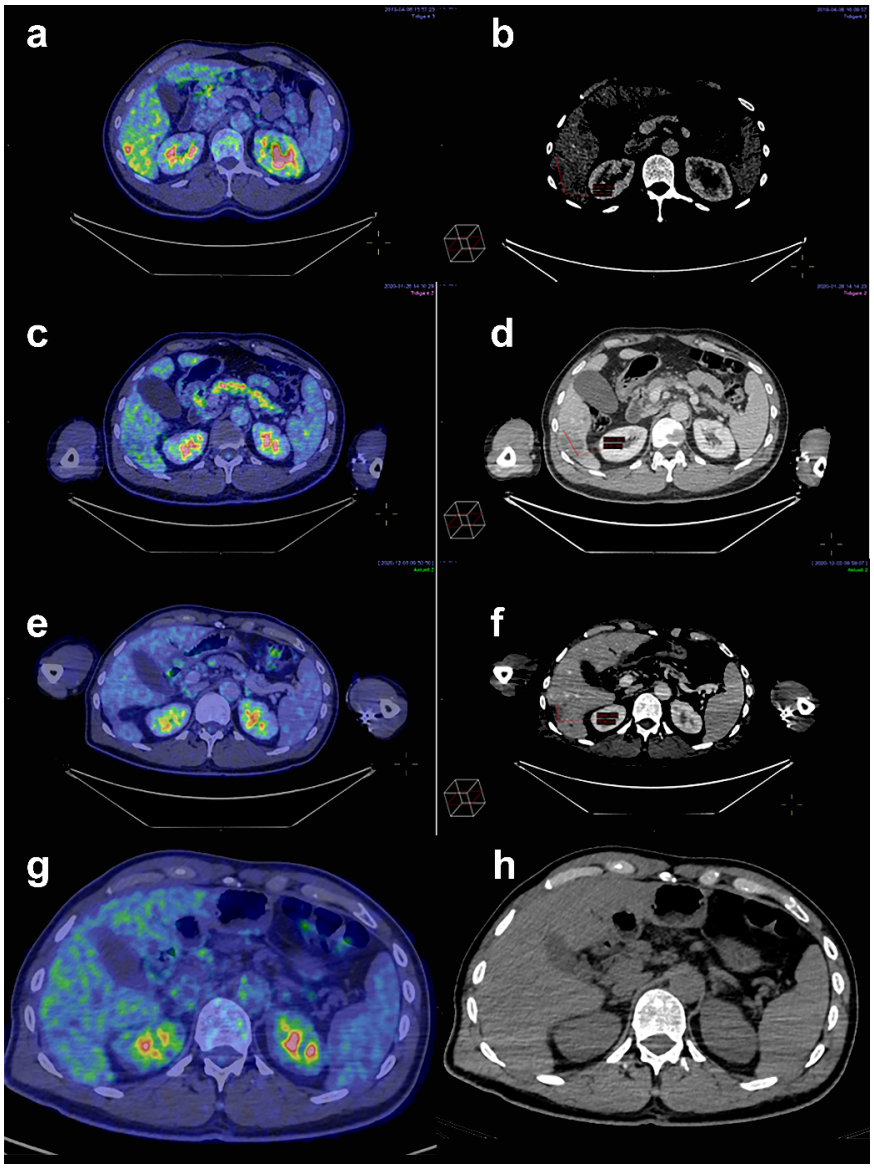

Figure 1: A 56-year old Caucasian man was diagnosed with metastatic uveal melanoma in April 2019. He underwent a baseline PET/CT scan at 6/4/2019 where a 50-mm according to RECIST 1.1 liver metastasis laterally dexter is visible both in the fusion image (1a) with a SUV max uptake at 5,9 and in CT image (1b). Treatment with NIVO3+IPI1 was initiated in May 2019. He received four such cycles followed by single nivolumab 480 mg every 4 weeks that was initiated in September, 2019. As shown in 1c there was no uptake in the fusion image (complete metabolic response CMR) in January 2020. The size of the metastasis in 1d was 40 mm. Since April 2020 due to the COVID-19 pandemic the patient received pembrolizumab 400 mg every six weeks instead of nivolumab. The treatment was paused in September 2020. In December 2020, ongoing CMR as shown in 1e, while the size of the metastasis was only 26 mm in 1f. At the latest PET/CT scan, in February 2021, was observed no evidence of metastatic disease nor in fusion images (1g) nor in CT images (1h).

patient underwent a PET/CT-scan evaluation every three months. In December 2020 PET/CT showed CMR and PR according to RECIST 1.1 (Figures 1e and 1f).

Two weeks after the initiation of the treatment with the combined immune checkpoint blockade the patient suffered from skin rash and urticaria on his torso, arms, face and his back (skin reaction of grade 1) as well as diarrhea (grade 1). He received hydrocortisone cream (group I steroid), antihistamine loratadine and loperamide with good effect. In April 2020, one year after the initiation of the treatment with immunotherapy, the patient experienced pressure over his chest. Electrocardiography and troponin were normal. Two weeks later, the skin rash recurred and the patient was again treated with hydrocortisone cream and loratadine. At the same time, he was suffering from right sided drop foot and was referred to the spine department since MRI revealed disc herniations. The herniations could not explain the clinical symptoms, so the patient was further referred to the neurology department. A lumbar puncture as well as a neurography test and an electromyography were performed, not showing any abnormalities. A new MRI of the spine was performed three months later without signs of deterioration and the drop foot symptoms were improved over time. During the summer period the patient complained of photosensitivity, i.e. pronounced erythema of the neck and the arms that was deteriorating over time. The photosensitivity was assessed as a suspect side effect and attempts with steroid cream of group III were made with sparse effect. Given the fact that the patient still experienced CMR after over one year and at the same time was suffering from photosensitivity it was decided to pause the PD-1 inhibitor treatment.

Although the treatment with the PD-1 inhibitor has been paused since the 1st of September the patient is still suffering from photosensitivity and diarrhea and needs loperamide on daily basis. A PET/CT scan was performed in February, 2021 and confirmed ongoing CMR and CR according to RECIST 1.1 as well (Figure 1g, 1h).

Discussion

We report on a patient with disseminated UM who has experienced long term benefit on treatment with the regimen NIVO3+IPI1. Complete metabolic response and PR were achieved seven and 18 months respectively after treatment start. The CMR has now remained for more than one year and the patient also experiences CR according to the most recent scan.

The most common ocular melanoma is the UM. Contrary to most other cancer types, treatment of mUM has not evolved much and mUM remains a great challenge in the field of oncology. After initial radiotherapy, surgery is the treatment of choice for locally recurrent disease. Half of the patients with UM will develop metastatic disease and then prognosis is fatal [3]. Recent meta-analyses of trials in mUM patients show a median OS of 10 months to 1 year [14-17]. Currently, there is no approved systemic therapy for mUM patients as no therapy has been shown to improve OS [18].

In some rare cases of oligometastatic disease, surgery, ablative procedures or stereotactic radiation therapy can be performed with curative intention [19]. There are no randomized trials comparing these methods with systemic therapy or best supportive care. Intrahepatic therapeutic approaches have been associated with responses that may add clinical benefit. Trials of isolated hepatic perfusion in patients with exclusively liver metastases showed promising results [20, 21]. Other treatment modalities have been evaluated including chemotherapy, immunotherapy, and molecularly targeted agents for the MAPK pathway.

There is no standard-of-care therapy, and participation in a clinical trial should be prioritized for patients with metastatic disease. For patients who cannot participate in clinical trials, the combined checkpoint blockade is a valid treatment alternative. A small number of observational and phase II studies suggest limited activity for combined immunotherapy with the NIVO1+IPI3 schedule in patients with mUM presenting response rates of 17%, median Progression-Free Survival (PFS) of up to 6 months, and median OS of up to 19 months [14,18,22,23].

Since our patient already suffered from both liver and bone metastases at diagnosis, local treatment was not an option. The treatment of choice at the time was temozolomide. Shortly after the initiation of this treatment, a new recommendation enabled switching to combined immunotherapy. LDH was >3 ULN at the initiation of the treatment and studies have shown that patients with an elevated LDH indicating a high tumor load are unlikely to respond. In addition, a low mutational burden is described in mUM while the probability of recognition by immune cells increases when mutational burden is high [24]. There are case reports on responses with PD1 inhibitory treatment in patients with mUM exhibiting a high number of mutations [25-27]. Our patient may have a tumour with high mutational load that could explain the CMR. However, an analysis of the number of mutations has not been carried out.

Najjar et al. conducted a retrospective analysis of 89 patients with mUM who received combined immunotherapy (NIVO1+IPI3). Complete response was achieved in one patient (1%). Median OS was 15 months and median PFS was 2.7 months. The majority of the patients discontinued treatment due to toxicity or Progressive Disease (PD). Common immune-related Adverse Events (AEs) were colitis/diarrhea (32%), elevated transaminases (21%) and rash (21%) [14]. Heppt et al. have in a retrospective, multi-center study reported 2 cases of CR among 64 patients who received either NIVO1+IPI3 or pembrolizumab+IPI1. Contact was made with the corresponding author who confirmed that both patients experiencing CR were treated with NIVO1+IPI3 [22]. Data from a prospective open-label trial investigating NIVO1+IPI3 were recently presented. One case with CR was confirmed among 33 patients. The median duration of response was 12 months while median OS was 19.1 months. Treatment-related AEs were diarrhea (60%), elevated transaminases (around 50%) and pruritus (40%). Almost one third of the patients discontinued treatment due to toxicity [28]. Piulats et al in a phase 2, multi-center have reported one case with CR after treated 52 patients with NIVO1+IPI3. Same profile regarding side effects as in the other studies [18].

In metastatic MM patients, Lebbé et al. showed that there were no difference in PFS between NIVO3+IPI1 and NIVO1+IPI3 while a significantly lower incidence of treatment-related grade 3-5 AEs were noted in the NIVO3+IPI1 group [10]. Furthermore, nivolumab 480 mg Q4W was shown to be equal to both nivolumab regimen 3 mg/kg Q4W and 240 mg Q2W [29]. Since these data were published the regimen NIVO3+IPI1 four cycles followed by maintenance with flat-dosing schedule of 480 mg Q4W has emerged as an alternative as a first-line treatment of patients with advanced melanoma in Sweden.

Our patient received NIVO3+IPI1 Q3W for a total of four doses, followed by nivolumab maintenance 480 Q4W that shifted to pembrolizumab 400 Q6W due to the COVID pandemic. The

patient achieved a PMR 12 weeks after treatment initiation while CR according to RECIST 1.1 was achieved over one year later.

The maintenance treatment was discontinued 16 months after treatment start due to long term CMR with minimal disease combined with toxicity. In patients with metastatic MM, there is some data regarding discontinuation of immunotherapy in the absence of PD or toxicity. When a CR is achieved and the patient has been treated for >6 months the risk of relapse after treatment discontinuation is low [30]. In our case, the treatment effect has even improved after treatment stop (see above).

The patient's general condition was considerably improved alongside with rapid regression of tumor lesions. The treatment was well tolerated except from diarrhea grade 1 requiring 2 mg of loperamide every day. He was treated for rash at two occasions with local steroids and antihistamines. Fourteen months after treatment initiation, our patient suffered from photosensitivity. This side effect is quite unusual and previous studies have reported that approximately 1% of patients treated with PD1-inhibitor develop photosensitivity [31]. Sarcoidosis-Like Reactions (SLR) induced by Checkpoint Inhibitors (CI) have been described with mediastinal lymph nodes being one of the most common locations. The reported median time between initiation of CI therapy and the development of a SLR is 14 weeks. There is evidence that the development of a CI-induced SLR indicates treatment efficacy and therefore should continue [32]. Our patient developed SLR in mediastinal lymph nodes 15 weeks after treatment initiation, he received no steroids and the treatment continued.

In two retrospective and two prospective studies on outcomes of totally 238 patients with mUM who received combined checkpoint blockade, only five cases of CR were observed. In these cases the patients were treated with NIVO1+IPI3, followed by nivolumab at 3 mg/kg Q2W as maintenance therapy [14,18,22,28]. Our patient received NIVO3+IPI1 while the maintenance therapy consisted of the flat-dosing regimen at 480 mg Q4W.

Conclusions

The patient with mUM described in this case report has clearly experienced long-term benefit from treatment with combined checkpoint blockade with no signs of relapse at latest follow up. To our knowledge this is the first described case of a patient with mUM experiencing CR on the NIVO3+IPI1 regimen having a superior safety profile compared to the NIVO1+IPI3 schedule registered for advanced MM.

Disclaimer

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Patient consent: The patient has given his consent for publication of this case report.

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