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Case Report

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Metastatic uveal melanoma complete response with nivolumab: A case report

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Abstract

Introduction: Uveal Melanoma (UM) is a rare subtype of melanoma that progresses to metastatic disease in more than 50% of patients [1]. After metastasis develops, the average survival is between 4-15 months [2].

The contribution of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein -1 (PD-1) targeted immune checkpoint inhibitors to Overall Survival (OS) is limited.

Case report: We report a case in which a patient diagnosed with UM with liver metastases had a complete response with the Anti-PD-1 Monoclonal Antibody Nivolumab for four years

Management and outcome: As liver metastases progressed under Temozolamide, Nivolumab 3 mg/kg/2 weeks was administered. Partial response was achieved in the third month of treatment, and complete response was achieved in the sixth month. The treatment of the patient has continued without major side effects for four years.

Discussion: In the literature, the rate of complete response with Nivolumab treatment in patients with UM is rare. Our case is of particular interest because of the complete response and the lack of majör side effects. Although the prognosis for UM with visseral metastases is poor, new treatment modalities may lead to long term survival.

Introduction

Uveal Melanoma (UM) is the most common intraocular malignant tumor in adults and a rare subtype of melanoma that progresses to metastatic disease in more than 50% of patients. Treatment options for local disease are radiation therapy or surgical approaches such as local resection and enucleation of the affected eye. Although these measures are highly effective for local tumor control, half of the patients develop systemic recurrence. Approximately 20-30% of patients diagnosed with primary uveal melanoma die due to metastasis within 5 years of diagnosis. Metastatic disease is the most common in the liver and has a poor prognosis, with an average survival of 4 to 15 months [3]. The development of immune checkpoint inhibitors targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death-1 (PD-1) has significantly improved the long-term prognosis for patients with advanced cutaneous melanoma. However, responses have been very limited in advanced UM. The lower number of somatic mutations in UM, the fact that it is a less immunogenic tumor, and the low number of neoantigens are suggested as the reasons for this [4].

Case report

A 57-year-old female patient presented with acute painless vision loss, defined as a sudden and rapidly progressive "vision loss" in her left eye. In the eye examination, a 1.1 cm lesion containing the ciliary body was detected. Complete blood count, biochemistry and LDH levels were found to be normal. Cranial MRI confirmed the lesion along the left retina and no other intracranial lesions were observed. PET/CT did not show uptake for metastasis. She underwent a curative-intent enucleation. The pathology result was ciliochoroidal malignant melanoma without extra scleral extension. In the third year of follow-up ; Lesions with suspected metastasis were observed. In addition, the LDH level was detected to be 350 U/L (The normal range is 105-333 U/L) in the blood tests. PET/CT showed uptake about liver metastases. The liver biopsy result is consistent with uveal melanoma metastasis and c-kit, BRAF or RAS mutations were not observed in molecular tests. Temozolamide treatment was administered. In the 3rd month of treatment, PET/CT showed uptake as a progressive disease (Figure 1). The patient in good general condition with ECOG PS:0 was treated with Nivolumab 3 mg/kg once every two weeks. No reaction was observed during the infusion. Grade 1 fatigue and hypothyroidism developed during the follow-up period. After endocrinology consultation, Levothyroxine replacement was administered. LDH levels began to decrease after Nivolumab treatment and were normal in the sixth week. Partial response was evaluated according to PET-CT in the third month of the treatment, and complete response was evaluated in the 6th month (Figure 2). In the fourth year of the follow-up and receiving the 105th infusion dose, the complete response is ongoing and additional side effects are not observed.

Discussion

In our case, we described a patient with metastatic UM, in whom we had a complete response with nivolumab treatment for four years and no major adverse effects were observed. Despite increasing knowledge of the genetics and pathophysiology of UM, treatment of metastatic disease remains a clear challenge.

UM treatment has wide range of outcomes. For instance, surgery and radiotherapy provide excellent local control of the disease. On the other hand, there is no proven treatment algorithm for patients who develop metastases.

Although classical chemotherapeutic agents are administered for cutaneous melanoma such as dacarbazine, temozolomide, cisplatin, treosulfan and fotemustine have been tried with various combinations, the results have not been satisfac-

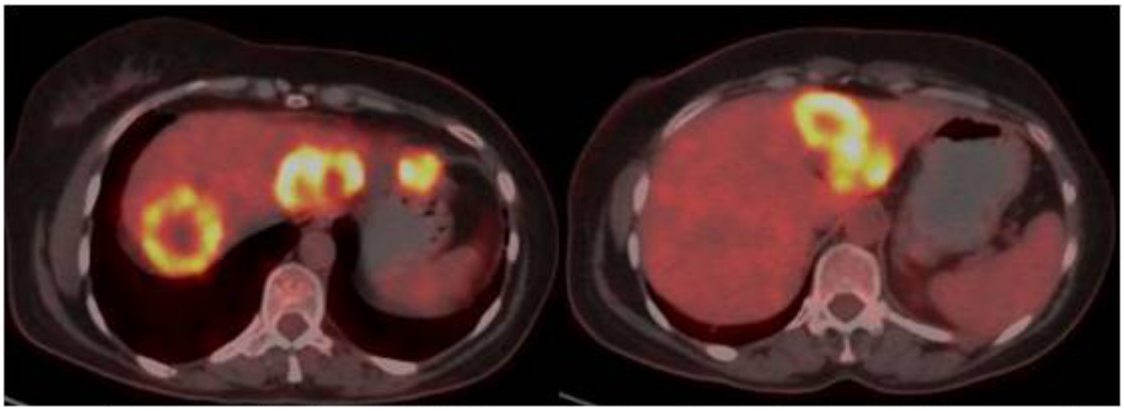

Figure 1: In the pre-treatment PET-CT examination of the patient. multiple lesions with increasd FDG uptake are observed in the liver, the largest of which is 52 mm in diameter in segement 7 (SUVmax: 11).

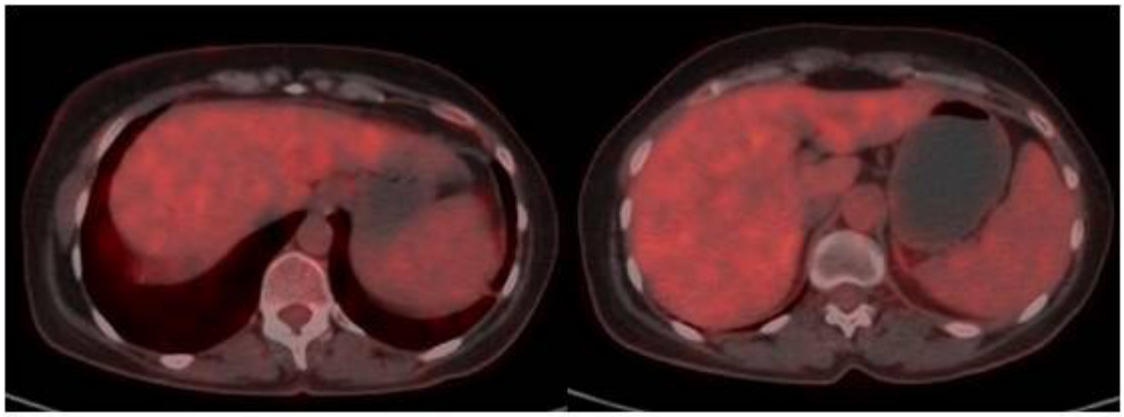

Figure 2: In the post-treatment PET-CT examination of the patient, lesions showing FDG uptake in the liver are not observed.

tory [5-8]. Response rates are 5-6%, with a mean survival of 6-12 months.

Nivolumab, an anti-PD-1 antibody, has been approved by the FDA for both metastatic and adjuvant therapy for cutaneous melanoma. In the literature, studies with immunotherapy in the treatment of metastatic uveal melanoma are limited, and there are phase 2 and retrospective studies involving a small number of patient groups. In a single-arm, open-label phase II study (CheckMate 172), the efficacy of Nivolumab was evaluated in approximately 1000 patients with advanced melanoma [9]. In the subgroup analysis of 103 patients diagnosed with UM, the median OS was 12.6 months and the 18-month OS rate was 34.8%.

In a retrospective study [10], 56 patients with metastatic UM refractory to previous treatments; PD-1 or programmed cell death ligand, including 38 patients (68%) were administered Pembrolizumab, 16 patients (29%) were administered Nivolumab, and 2 patients (4%) were administered Atezolizumab (PD-L1 inhibitors). Objective tumor responses were observed in 2 patients for an overall response rate of 3.6% (95% confidence interval [CI], 1.8%-22.5%). Stable disease (≥6 months) was observed in 5 patients (9%). The median Progression-Free Survival (PFS) was 2.6 months (95% CI, 2.4-2.8 months), and the median OS was 7.6 months (95% CI, 0.7-14.6 months). Based on these studies, immunotherapy is recommended in guidelines.

In patients with treatment-naive metastatic UM, the use of single-agent cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors is less preferable than single-agent PD-1 inhibitors. Phase II studies with İpilimumab and Tremelimumab showed limited efficacy and more immune-related side effects were reported in patients [11,12].

Combination studies have been performed after obtaining significant results with CTLA-4 inhibitors and anti-PD-1 inhibitors as monotherapy. It has been shown that the combination of Nivolumab and Ipilimumab has better results compared to single-agent immunotherapy agents in OS and ORR. In the phase II study in which 33 patients were evaluated; according to the ORR it was 18%, including one confirmed complete response and five confirmed partial responses. The median PFS was 5.5 months (95% CI, 3.4 to 9.5 months), and the median OS was 19.1 months (95% CI, 9.6 months to NR) [13]. The results are the opposite of the dramatic efficacy observed in patients with metastatic cutaneous melanoma. Similar results were obtained in another phase II study, The median OS and PFS were found to be 12.7 months and 3.0 months [14].

In patients diagnosed with metastatic UM, human leukocyte antigen (HLA)-A*02:01 genotyping assay is recommended before starting systemic treatment, after demonstrating the effectiveness of Tebentafusp in the study. Tebentafusp is an affinity-enhanced bispecific protein fused to an anti-CD3 effector that can direct T cells to target glycoprotein 100-positive cells. In the study of 378 patients, patients were assigned a 2:1 ratio of Tebentafusp or single-agent Pembrolizumab, İpilimumab, or Dacarbazine arms. At the end of the 14-month follow-up period; Tebentafusp improved OS, one-year OS 73 versus 59 percent; median OS 22 versus 16 months (15). With these results, FDA approved, HLA-A*02:01-positive adult patients with metastatic uveal melanoma.

The most important molecular targets for cutaneous melanoma are BRAF and MEK; however, UM lacks BRAF mutations because the RAS-ERK pathway is constitutively activated by GNAQ/GNA11 mutations. In addition, MEK inhibitors used in the treatment of cutaneous melanoma are not recommended as they have a different molecular pathogenesis from UM cutaneous melanoma and data shows limited efficacy for these agents. A phase II study evaluating the MEK inhibitor selumetinib versus chemotherapy showed a moderate improvement in PFS, but no OS benefit [16].

Trametinib, another MEK1/2 inhibitor, showed limited clinical activity in 16 treated patients with metastatic UM. While the median PFS corresponded to 1.8 months, the response rates were zero as no relevant radiological response was observed [17].

The use of immune checkpoint inhibitors may lead to the development of adverse events and toxicities. The frequencies of immune-related adverse event (iRAE) effects are higher for the combination of PD-1 and CTLA-4 agents than for either of these treatments alone. Toxicity in the gastrointestinal tract, liver, skin and endocrine system is common. In a phase III study (CheckMate 067), grade 3 or 4 iRAEs occurred in 55% of the combination group, 16% and 27% for Nivolumab and İpilimumab alone, respectively [18].

Conclusion

In this case of metastatic UM, no major adverse events were observed and a complete response was obtained with Nivolumab. The average response to the treatment was observed at around 12 months in these studies, However, the absence of adverse effects during four years of Nivolumab treatment followed by a complete response may guide future treatment methods.

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