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Case Report Open Access

Simultaneous Treatment of Severe Vemurafenib-induced Uveitis and Metastatic Melanoma

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Abstract

Background: Vemurafenib, a serine-threonine kinase inhibitor, has been used to treat unresectable metastatic melanoma since 2011. Ocular adverse events are reported to be seldom and to regress after the discontinuation of vemurafenib and therapy with topical steroids. However, this approach must be weighed against the potential progression of melanoma. We present alternative options in uveitis treatment enabling the continuation of vemurafenib therapy.

Case report: We describe the clinical course of vemurafenib-induced uveitis in two patients initially presenting with macular oedema and scleritis. Both patients were treated successfully without discontinuing vemurafenib. Intraocular inflammation and macular oedema receded slowly after intraocular injection of 700 mg dexamethasone into the first patient's right eye. A moderate rise in intraocular pressure was controlled easily with topical anti-glaucomatous treatment. Since the intraocular inflammation had not abated under topical steroids, dexamethasone was injected into the left eye also. The second patient presented with intraocular inflammation and severe scleritis in both eyes, and was treated systemically with 80 mg prednisolone p.o. per day. His ocular condition and visual acuity improved quickly. The macular oedema receded completely in both eyes.

Conclusion: In patients with vemurafenib-induced uveitis, the progression of melanoma must always be weighed against the alleviation of ocular symptoms. We suggest a priori systemic or intravitreal steroid treatment with simultaneous anti-melanotic therapy. Intravitreal treatment should be considered in case of macular oedema. Systemic and topical steroid therapy requires slow tapering to prevent a relapse of ocular inflammation.

Keywords: Uveitis; Vemurafenib; Ozurdex; Melanoma; BRAF

Introduction

Vemurafenib (Zelboraf®, F. Hoffmann-La Roche Ltd, Basel, Switzerland), a serine-threonine kinase inhibitor, was approved for the treatment of unresectable metastatic melanoma with proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B (BRAF) V600 mutation in 2011. The V600E mutation accounts for 80% of all BRAF mutations, which are found in 40% to 60% of all melanomas [1]. Mutations of the gene encoding for serine-threonine kinase BRAF result in its permanent activation and unregulated cell growth [2].

The most common adverse events of vemurafenib therapy are arthralgia (53%), alopecia (45%), fatigue (38%), nausea (35%) and photosensitivity (33%) [1]. In contrast, the incidence of ocular adverse events is reportedly low. The US Food and Drug Administration provides data on adverse drug reactions based on an international, randomised, open-lable and a single-arm multicentre, multinational trial [3]. Uveitis occurred in 2.1% of the study patients, five patients reported blurred vision (1.5%) and six patients suffered from photophobia (1.8%) [4]. There was one case of retinal vein occlusion [5]. Though Sandhu et al. reported a slightly increased risk of uveitis under vemurafenib, clinical experience in treating ocular adverse events is rather sparse. Topical or systemic treatment with steroids leads to recovery in many cases [2, 6]. However, discontinuation of vemurafenib was recommended by some authors, especially in severe cases of uveitis [4, 7], putting the patient at risk of melanoma progression [7]. In a review of clinical study reports from clinical pharmacology phase 1, 2, and 3 trials, Choe et al. found that uveitis was the most common ocular adverse event in 568 patients treated with vemurafenib (4%). It is remarkable that all these adverse events were reported to have been successfully managed without discontinuing vemurafenib therapy [8].

We would like to make a contribution to this controversial discussion by describing different treatment approaches and for the first time report on the effect of intravitreal dexamethasone (OZURDEX®, Allergan, Inc., and Irvine, CA, U.S.A.) implantation in patients with vemurafenib-induced uveitis.

Case Report

Case 1 In January 2013, a 49-year-old male patient presented with a batch-wise, progressive loss of visual acuity in the right eye. He had no history of ocular problems. Malignant melanoma on the left calf had been diagnosed in 2006. After initial therapy with interferon-alpha, the patient underwent local excision of cutaneous metastases and consecutive irradiation. Multiple lymph nodes were excised in 2010

and 2011 due to metastatic progression, and in 2011 vemurafenib therapy was initiated.

His initial visual acuity was LogMAR 0.3 in the right and LogMAR 0.00 in the left eye. Slit lamp biomicroscopy revealed a fibrino-cellular reaction in both anterior chambers with positive flare and vitreal cellular infiltration. Spectral-domain optical coherence tomography (SD-OCT) revealed cystoid and subretinal macular oedema in the right eye.

We started binocular topical treatment with prednisolonacetate 10 mg/mL t.i.d. and injected dexamethasone (700 µg) intravitreally into the right eye. Upon his follow-up examination two weeks post-injection, we noted an improvement in visual acuity to LogMAR 0.10 and corresponding regression of the macular oedema. Intraocular pressure had risen to 27 mmHg in the right eye. We initiated local therapy with brimonidine[(R,R)-tartrate] 2 mg/mL in combination with timolol 5 mg/mL b.i.d. His intraocular pressure a week later was within normal limits.

In February 2013, his visual acuity was LogMAR 0.00 and the intraocular inflammation had completely receded in the right eye. Visual acuity in the left eye had deteriorated to LogMAR 0.60. Both anterior chambers were clear. SD-OCT revealed macular oedema in both eyes with further regression in the right eye. We opted to inject dexamethasone intravitreally into the left eye also. Three weeks later, visual acuity was LogMAR 0.20 and the patient was referred to his local ophthalmologist for regular check-ups. No relapse has been reported so far.

Case 2 In January 2013, a 63-year-old male patient presented with progressively worsening visual acuity in the right eye, present for about a week. He was also suffering from photophobia and pain deep behind the left bulb. Treatment with prednisolonacetate 10 mg/mL q.i.d. had not attenuated the patient's discomfort. He had reported an episode of ocular inflammation about one year before. Beyond that, he had no history of ocular problems. He had already undergone cataract extraction in both eyes. A history of amblyopia in the right eye could not be definitively ruled out.

A malignant melanoma on his back had been diagnosed in August 2010. He had undergone radical lymphadenectomy of the right axilla in 2011. Six months of interferon-alpha therapy was abandoned due to persisting thrombocytopenia. Vemurafenib was initiated in March 2012 because of intracerebral, mediastinal, bihilary, intrapulmonary, and hepatic metastases. Multiple cutaneous squamous cell carcinomas were completely resected except for one carcinoma in the neck (R1). Because of haematological adverse events, that treatment had to be discontinued in early February 2013. Since the intracerebral metastases were progressing, cerebral radiation was initiated and vemurafenib therapy restarted in May 2013.

The patient reported having a 40-pack-years smoking history. He had undergone a tonsillectomy in 1973 and appendectomy in 1960.

Visual acuity was initially LogMAR 0.30 in the right and LogMAR 0.10 in the left eye. Ciliary injection was present in the left eye. Slit lamp biomicroscopy revealed fibrino-cellular infiltration and fresh endothelial precipitates in both eyes, and snowballs in the right eye only. Vascular sheathing was present bilaterally and the papillae appeared slightly hyperaemic. SD-OCT revealed subretinal oedema in the right and cystoid oedema in the left eye. Topical treatment was intensified by applying 10 mg/mL prednisolonacetate seven times per day. Nevertheless, his visual acuity had deteriorated to LogMAR 0.90 in the right eye a week later and anterior and vitreal cellular infiltration had increased. The findings in the left eye had not changed. Due to severe scleral inflammation, intravitreal steroid injection turned out to be too painful. We therefore decided on systemic treatment with 80 mg prednisolone p.o. per day and reduced the frequency of topically administering 10 mg/mL prednisolonacetate to q.i.d.

After four days of treatment, visual acuity was LogMAR 0.30 and LogMAR 0.20, respectively. The binocular intraocular inflammation, pain, and photophobia in the left eye had diminished slightly. Systemic therapy was continued for five more days and afterwards reduced to 60 mg p.o. per day. Topical therapy with 10 mg/mL prednisolonacetate was reduced to t.i.d. Visual acuity exhibited further improvement to LogMAR 0.10, thus we decided to slowly reduce the systemic treatment (over a 10-week period). On follow-up, his visual acuity was LogMAR 0.00 in both eyes. Slit lamp biomicroscopy showed minor vitreous cellular infiltration. The macular oedema had completely receded in both eyes. In May 2013, the patient's general constitution had improved so much that vemurafenib could be continued. However, in early 2014 he presented with a sudden deterioration in visual acuity to LogMAR 0.90 in the right eye. Slit lamp biomicroscopy revealed pronounced cellular infiltration of the anterior chamber and the vitreous. Accordingly, SD-OCT imaging of the macula was impossible. We re-started systemic treatment with 60 mg prednisolone p.o. per day, tapered slowly over a seven-week period. Vemurafenib therapy was not interrupted. Two weeks later there were no signs of inflammation and visual acuity had increased to LogMAR 0.00 in the right eye.

The course and clinical signs in both these patients make it highly unlikely that their uveitis was of paraneoplastic, metastatic, or idiopathic etiology.

Discussion

Drug-induced uveitis used to be considered a rare complication [8,9]. However, the frequency of drug-induced uveitis has risen continuously during the last few years due to the introduction of new drugs such as biologic agents or new bisphosphonates [10]. The relevant pathogenetic mechanisms are still not completely understood [8]. Both toxic and inflammatory reactions have been discussed [7,11,12]. Clinical observations suggest that there is a strong association between the intake of vemurafenib and the occurrence of ocular inflammation, which might be due to the response on subclinical metastatic cells within the uvea or to the erroneous interaction of vemurafenib with antigens shared by melanocytes and the choroid. Onset of the initial symptoms is reportedly 27 weeks (range: 1 to 85 weeks) on average after the first treatment. Choe et al. reporting of cases of recurrent uveitis under continued vemurafenib therapy, indicate a median of 117 days (range 7 to 550 days) [8]. The anterior uvea is primarily affected [6]. Accordingly, topical steroid application usually suffices if anti-melanotic treatment is discontinued [10]. However, there are reports of severe cases of uveitis associated with vemurafenib. Wolf et al. reported on a 63-year-old patient with panuveitis and almost total vision loss. The anti-melanotic therapy was discontinued and steroids were applied systemically. The visual symptoms improved, but the patient died of progressive cerebral metastases [7]. Since the discontinuation of vemurafenib in such situations must be weighed carefully against the possibility of melanoma progression, it is crucial to devise alternative treatment approaches. We report on two patients not responding to topical steroids because of both anterior and posterior uvea involvement. Since macular oedema was present, and to avoid systemic adverse

events, we decided on intravitreal injection of dexamethasone in case one. Both therapeutic strategies turned out to be effective. However, intravitreal therapy should be considered the first-line strategy if macular oedema is diagnosed. As Urner-Bloch et al. claim regarding mitogen-activated protein kinase (MEK) inhibitor-associated retinopathy [13], we suggest that a priori discontinuation of vemurafenib should be avoided whenever possible, and that the set-up of a multidisciplinary treatment schedule is inevitable. The ocular condition of the patient who had undergone systemic steroid therapy worsened about nine months after stopping the ocular treatment. We therefore recommend slowly tapering systemic or topical steroids as well if the patient is free of symptoms.

Lemech and Artenau refer to findings suggesting a reduction in the incidence of adverse events such as rash, hyperproliferative skin lesions, and squamous cell carcinoma via simultaneous treatment with BRAF inhibitors and MEK inhibitors [2]. It will be up to future studies to prove whether this regime is effective in reducing the incidence of ocular side effects as well.

Conclusion

Considering the beneficial effect of vemurafenib on melanoma's prognosis, we suggest treating vemurafenib-induced uveitis with intravitreal or systemic steroids and continuing the anti-melanotic therapy even in patients presenting severe inflammation. Only mild manifestations of vemurafenib-induced uveitis may resolve after topical steroid application. Intravitreal steroids might be more beneficial, especially in case of macular oedema. Systemic and topical steroid therapy must be slowly tapered to prevent a relapse of inflammation.

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