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Radiation necrosis mimicking rapid intracranial progression of melanoma metastasis in two patients treated with vemurafenib

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Abstract

Optimal treatment of metastases to the central nervous system (CNS) in patients with malignant melanoma remains a clinical challenge. In particular, for patients with *BRAF*-mutant melanoma and CNS metastases, much remains unknown about the safety and efficacy of the novel *BRAF*-targeted agents when administered in close sequence with radiation. We report two cases of rapid development of CNS radiation necrosis in patients with metastatic melanoma treated with the *BRAF* inhibitor, vemurafenib, closely sequenced with stereotactic radiosurgery or fractionated stereotactic radiation therapy. In the absence of prospective safety data from clinical trials, we advise vigilance in monitoring patients with *BRAF*-mutant melanoma whose treatment plan includes CNS radiation and vemurafenib and caution when assessing treatment response within the CNS in these patients.

Keywords

BRAF inhibition; brain metastases; melanoma; radiation necrosis; radiation therapy; stereotactic radiosurgery; vemurafenib

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Conflicts of interest

For the remaining authors there are no conflicts of interest.

Introduction

Over one-third of all patients with advanced melanoma will be diagnosed with metastases to the brain during the course of their disease [1]. Central nervous system (CNS) metastases have historically been associated with a poor prognosis, although incorporation of surgery and radiation therapy (RT) as part of a multimodality approach has been associated with improved overall survival in nonrandomized pooled data analyses [2]. Twelve-month local control rates range from 68 to 80% with stereotactic radiosurgery (SRS) alone [3,4], and up to 90% with RT following surgical resection [5].

The advent of targeted therapies for patients with advanced *BRAF*-mutated melanoma has led to growing interest in evaluating the efficacy of vemurafenib and other BRAF inhibitors in patients with metastatic melanoma to the CNS [6]. Despite theoretically poor drug bioavailability in the CNS, early case reports did suggest activity of vemurafenib in selected patients with CNS metastases [7–9]. However, for the majority of patients with *BRAF*-mutated metastatic melanoma, CNS progression continues to be problematic, even when responses to vemurafenib therapy outside the CNS are significant and durable. For these patients, data on the safety and efficacy of vemurafenib when administered concurrently or sequentially with RT are unfortunately still quite limited, with conflicting data from published case studies [10–14]. We present two cases of rapid development of CNS radiation necrosis in patients with metastatic melanoma treated with the BRAF inhibitor, vemurafenib, closely sequenced with SRS or fractionated stereotactic radiation therapy (FSRT).

Case 1

A previously fit 22-year-old man initially presented to our Multidisciplinary Melanoma Clinic for evaluation and treatment of a *BRAF*-V600E-mutant stage IIIA melanoma of his upper back. Definitive therapy consisted of wide-excision, sentinel lymph node biopsy followed by left axillary node dissection, and 1 year of adjuvant high-dose interferon $\alpha 2b$. Four years after his initial diagnosis, he was diagnosed with a second primary melanoma, stage IIIC, located on the scalp. He was treated with wide-excision and complete neck dissection. He declined adjuvant high-dose interferon $\alpha 2b$ at this time and elected to pursue off-label therapy with adjuvant granulocyte–macrophage colony stimulating factor. Unfortunately, 10 months after starting granulocyte–macrophage colony stimulating factor, he developed acute headaches and was diagnosed with a large 2.5 by 2.4 by 2.9 cm hemorrhagic metastasis to the right frontal lobe. Staging scans also confirmed numerous intra-abdominal and subcutaneous lesions consistent with metastatic disease. Resection of the frontal lobe lesion confirmed metastatic melanoma, positive for the *BRAF*-V600E mutation.

His postoperative MRI also showed a small 4 mm lesion in the left frontal lobe. The resection cavity was treated with 2700 cGy in three fractions with FSRT, and the left frontal lobe lesion was treated with SRS with 2200 cGy in one fraction (Fig. 1a). He was started on temozolomide 150 mg/m² days 1–5 on a 28-day cycle beginning with his second dose of FSRT. One month following completion of radiation, he reported increasing headaches. A

repeat MRI demonstrated interval hemorrhage and enlargement of the left frontal lobe lesion, now measuring 2.2 by 1.8 cm. He discontinued temozolomide and received an additional 2400 cGy in four fractions with FSRT to this lesion (Fig. 1b). He was started on vemurafenib 960 mg twice daily 1 week after completing RT. He tolerated vemurafenib well with regression of his cutaneous and visceral metastases. However, 6 weeks after starting vemurafenib, he developed recurrent severe headache. MRI of the brain showed marked enlargement of a rim-enhancing left frontal lesion (2.7 by 2 by 4 cm) with associated edema and subfalcine herniation (Fig. 1c and d). He underwent craniotomy and resection of the left frontal lesion; final pathology showed necrosis only with no viable tumor (Fig. 1e and f). He recovered well from surgery and resumed vemurafenib postoperatively. Unfortunately, he was not able to tolerate a dexamethasone taper because of worsening headaches. A follow-up MRI of the brain was consistent with progressive radiation necrosis, which required maintenance dexamethasone for symptom management. Vemurafenib was discontinued. He subsequently developed systemic disease progression and was treated with dabrafenib 150 mg twice daily and trametinib 2 mg daily, but expired shortly thereafter from disease progression.

Case 2

A 35-year-old man with no significant prior medical history presented to our Multidisciplinary Melanoma Clinic for management of a *BRAF*-V600E-mutant stage IIC spindle-cell melanoma of the back. He was treated with wide-excision, sentinel node biopsy, and completed 1 year of adjuvant high-dose interferon α 2b. Forty-four months after his initial diagnosis, he was diagnosed with metastatic melanoma of the lungs and lymph nodes. He was initially treated with temozolomide for 9 months, followed by carboplatin and paclitaxel for an additional 9 months. Carboplatin and paclitaxel was held for myelosuppression and neuropathy. He then commenced treatment with vemurafenib 960 mg twice daily, with regression of his pulmonary metastases. However, 3 months after starting vemurafenib, MRI of the brain showed development of a 2.2 by 2.7 cm left frontal lobe metastasis. Vemurafenib was held, and he underwent craniotomy and resection of the lesion 1 day later; pathology was consistent with metastatic melanoma. Postoperative FSRT was administered to the resection cavity in five 600 cGy fractions (3000 cGy) beginning 3.5 weeks after surgical resection (Fig. 2a). He restarted vemurafenib 2 weeks after completing RT. Four months following completion of RT, he developed worsening headaches. Repeat MRI documented increased enhancement and vasogenic edema at the site of the prior resection (Fig. 2b). He was treated with dexamethasone, which provided symptomatic benefit. However, on follow-up MRI, worsening vasogenic edema and contrast enhancement was noted, raising the concern for possible tumor progression (Fig. 2c and d). Vemurafenib was held, and the intracranial lesion was resected. Pathologic review identified necrosis only, with no viable tumor (Fig. 2e and f). Following resection, he continued to have progressive edema around the resection cavity. Two months after his re-resection he was admitted with new-onset seizures, which were treated with dexamethasone and levetiracetam. Five months postresection, he developed acute personality changes, aphasia, and ataxia associated with progressive cerebral edema, which was corticosteroid refractory. He was treated with bevacizumab 7.5 mg/kg, three doses every 3 weeks time, with an

excellent durable clinical and radiographic response and is now under observation and off corticosteroids. However, he does have residual difficulty with speech and thought processes. Vemurafenib has been on hold since his surgery and he has no evidence of active systemic disease.

Discussion

To the best of our knowledge, these two cases represent the first reports of pathologically confirmed CNS radiation necrosis in patients treated with vemurafenib and radiation. In both cases, treatment was not administered concurrently; instead, patient 1 completed RT 1 week before initiating vemurafenib, and patient 2 did not resume taking vemurafenib until 2 weeks after completion of radiation. Both patients developed rapid onset of symptomatic radiation-induced necrosis 3 and 4 months, respectively, following their initial radiation treatment.

Preclinical work has shown that vemurafenib can function as a radiosensitizing agent in both tumor and normal tissues, likely by altering cell survival signaling and DNA damage responses that are normally modulated by the MAPK pathway [15,16]. Clinical observations support the notion of vemurafenib as a radiosensitizer, with unexpected radiotoxicity having been described in patients treated with sequential or concurrent vemurafenib and RT. Satzger and colleagues documented three cases of severe skin toxicity in patients treated with concurrent vemurafenib and radiation, and Anker and colleagues recently reported a case of severe, fatal liver toxicity in a patient treated with RT to the thoracic spine closely sequenced with vemurafenib [12,13]. A retrospective study of 12 patients treated with vemurafenib and whole brain, partial brain, or SRS identified one case of CNS radiation necrosis by radiographic imaging in a patient treated with vemurafenib and SRS; her case was notable for a history of prior treatment with concurrent temozolomide and partial-brain irradiation [14]. The remainder of patients in this series tolerated combination therapy relatively well, with the radiographic response rate of the index lesions in this series at 75% (48% complete response; 27% partial response) and the 6-month local control rate and freedom from new brain metastases being 75 and 57%.

These cases raise several questions concerning the optimal timing and sequencing of vemurafenib and RT in patients with metastatic melanoma to the CNS. Despite the growing understanding of MAPK pathway activation as an important modulator of cellular response to radiation damage, much remains unknown about the cellular dynamics of MAPK activation following RT. In the absence of prospective data, it is reasonable to surmise that radiation dose per fraction, cumulative dose, and tissue treated are all important factors determining the degree and duration of MAPK pathway activation following radiation. Prolonged modulation of MAPK signaling, or signaling through associated pathways, may explain the toxicity seen in our patients, even though vemurafenib was held during radiation and they did not receive concurrent therapy. We further surmise that patient-specific variations in drug metabolism and DNA damage repair may be important modulators of vemurafenib–radiation interactions, and can potentially account for unexpected severe toxicities in a subset of patients.

Several prospective studies should provide us with some information on which to base clinical decision making going forward. A phase 2 study of vemurafenib as primary therapy in patients with *BRAF*-mutant melanoma and active CNS metastases has completed accrual (NCT01378975) and will provide a baseline for understanding clinical activity of vemurafenib monotherapy for patients with *BRAF*-mutant metastatic melanoma to the CNS. Additional prospective studies should shed light on the potential interactions between RT and vemurafenib: NCT01781026 is a phase 2 study of vemurafenib administered as neoadjuvant therapy for patients with CNS metastases before surgery, ablation, or radiation, and NCT01843738 is a phase 1 study of concurrent radiation and vemurafenib for patients with active intracranial or extracranial disease.

We acknowledge a potential confounding factor of temozolomide therapy in our first patient in close proximity to his initial course of radiation, although the treatment schedule he received has typically not been associated with increased risk of radiation necrosis [17,18]. We also acknowledge that it is possible that CNS necrosis could be induced solely by the RT without pharmacologic interplay. However, the biologic effective dose of radiation received following SRS in our first patient (72 Gy³) parallels doses administered before SRS on RTOG-9508 (biologic effective dose 68.75 Gy³), and dosing of FSRT to our second patient (90 Gy³) is similar to several FSRT reports [19,20]. Rates of radiation necrosis would not be expected to exceed rates reported in these studies, which were 3% at 6 months and 8% at 9 months, respectively.

Conclusion

These two cases represent the first reports of pathologically confirmed CNS radiation necrosis in patients treated with closely sequenced radiation and vemurafenib. The onset of symptoms was rapid, occurring at 3 and 4 months, respectively, following treatment. These cases highlight the fact that not all progressive lesions identified on CNS imaging in patients with metastatic melanoma are secondary to progressive disease. In point-of-fact, no viable tumor was found on pathologic evaluation of both of these cases. In the absence of safety and efficacy data from prospective trials, we advise vigilance in monitoring patients with *BRAF*-mutant melanoma whose treatment plan includes CNS radiation and vemurafenib and caution when assessing treatment response within the CNS in these patients.

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Fig. 1.

Central nervous system imaging, radiation dose distribution, and histopathology for patient 1. (a) Postcontrast MRI before fractionated stereotactic radiation therapy to the surgical bed of the right frontal lobe and stereotactic radiosurgery to the new left frontal lesion (treatment 1). (b) Postcontrast MRI before fractionated stereotactic radiation therapy to the area of hemorrhagic conversion of the left frontal lobe lesion with increased size, includes dose contribution of treatments 1 and 2. (c) Postcontrast MRI of increased rim-enhancing lesion with surrounding edema. (d) FLAIR showing increased edema and overlying radiation dose distribution. (e) Photomicrograph of case 1 showing sheets of necrotic debris and a necrotic hyalinized vessel demonstrating radiation-induced changes (arrowheads) (H&E, × 200). (f) Higher magnification demonstrating necrotic ghost cells (arrow) and a necrotic hyalinized vessel with radiation-induced changes (arrowheads) (H&E, × 400).

Fig. 2. Central nervous system imaging, radiation dose distribution, and histopathology for patient 2. (a) Postcontrast MRI of surgical bed with residual postsurgical enhancement around the cavity. (b) Postcontrast MRI showing increased size and thickening of enhancement as well as increased surrounding vasogenic edema concerning for progression. (c) Postcontrast MRI showing interval increase of abnormal contrast enhancement and vasogenic edema. (d) T2 FLAIR displaying progression of vasogenic edema. (e) Photomicrograph showing necrosis, an axonal spheroid (arrow) and a hyalinized vessel (arrowhead) (H&E, $\times 200$). (f) Higher magnification demonstrating a hyalinized vessel with radiation changes, surrounding hemosiderin (arrows) and microcalcifications (arrowhead) (H&E, $\times 400$).