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Case Report

Vemurafenib Treatment of BRAF V600E–Mutated Malignant Peripheral Nerve Sheath Tumor

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Abstract

No effective systemic treatment exists for malignant peripheral nerve sheath tumors (MPNSTs). These tumors have been reported to show increased activity in the mitogen-activated protein kinase pathway from the loss of neurofibromatosis-1 regulation and occasionally from *BRAF* V600E mutation. A patient with sporadic metastatic MPNST and the *BRAF* V600E mutation was treated with standard doses of sorafenib and later vemurafenib and followed for response. The patient showed a rapid but modest and transient response to sorafenib and a very dramatic response to vemurafenib. This case represents the first report of successful systemic treatment of MPNST with an inhibitor of the *BRAF* V600E mutation. It will be important to define the general utility of this approach and related therapies in this disease. (*JNCCN* 2013;11:1466–1470)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Evaluate treatment options for patients with malignant peripheral nerve sheath tumors
- Discuss the potential benefits of vemurafenib in the presence of a *BRAF* mutation

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Novel Treatment of Malignant Peripheral Nerve Sheath Tumor

Malignant peripheral nerve sheath tumors (MPNSTs) are uncommon cancers that can demonstrate extremely aggressive behavior. Primary treatment involves surgical removal, which often is not curative and may result in significant disability. Radiation therapy can be of some utility, whereas systemic chemotherapy has been largely unhelpful. Much effort has recently been devoted to analysis of the genomes of these tumors in an effort to develop new useful therapies for this disease. This article describes the dramatic results of a novel approach to the treatment of MPNST.

Case Report

SC is a 51-year-old white woman who presented in August 2011 with a mass high in the right axilla. Scans revealed no other signs of disease. At surgical resection the mass was 8.7 cm in diameter and intimately associated with the brachial plexus. Thirteen lymph nodes were negative for tumor. Pathology showed a spindle cell neoplasm consistent with a MPNST. Histochemical staining showed a subset of epithelioid cells with S-100 positivity. There was some focal staining for desmin. Pankeratin, CD31, CD34, TLE-1, HMB-45, and EMA were negative. The diagnosis was confirmed on extramural pathologic review. No findings or family history suggested neurofibromatosis. Postoperative radiation was given to a dose of 4600 cGy over 23 fractions.

In August 2012 the patient felt a swelling on the left shoulder. Scans showed a 3.4-cm mass in the head of the humerus. PET/CT scan showed no other disease. The lesion was resected with the help of preoperative embolization.

In November 2012, the patient noted multiple subcutaneous masses on the skin of the chest wall and abdomen, and a recurrence at the site of the left shoulder metastasis. These ranged in size from a few millimeters to more than 3 cm in diameter. A CT scan also showed adrenal metastases. Genomic evaluation showed no abnormalities regarding *BRCA*; *cMET*; *EGFR*; *SPARC*; estrogen, progesterone, and androgen receptors; *HER2*/neu; *PI3K*, and *PTEN*. However a *BRAF* V600E mutation was demonstrated. The patient's health insurance carrier was willing to authorize treatment with sorafenib but not vemurafenib. Treatment with sorafenib was initiated in December 2012. A rapid but modest shrinkage of

many of the cutaneous tumors was seen in the first 10 days of treatment. At that point, disease activity stabilized. However, within 4 weeks of the initiation of sorafenib therapy, a rapid and dramatic increase in tumor growth occurred with innumerable new metastases on the skin of the thorax and abdomen, many of them exceeding 5 cm in diameter. Particularly extensive growth occurred at the site of the left humeral metastasis (Figure 1) and on the skin over the left scapula, where a 12-cm subcutaneous tumor was noted. Additionally, a 9-cm metastasis was noted on the skin just below the left breast and a 6-cm lesion was found on the skin on the right upper abdomen. A 5-cm tumor was evident on the left posterior neck. Many of these tumors were painful.

In March 2013, insurance approval was obtained for the use of vemurafenib and treatment with this drug was begun at 960 mg twice daily. Within 4 days, all visible tumors had decreased in size. By day 12, the 12-cm left scapula tumor was reduced to 5 cm in diameter. The left shoulder tumor had shrunk by approximately 50% with liquefaction evident on exam. The skin lesions on the abdominal wall were 4 and 3 cm, respectively. The left posterior neck tumor was 3 cm.

During the third week of treatment, the patient experienced rapid onset of a macular erythematous rash that quickly grew to cover approximately 90% of her body. This was accompanied by daily fevers ranging from 102°F to 103°F. A search for an infectious origin proved fruitless. Vemurafenib was discontinued on day 17 and the patient received 6



Figure 1 Pretreatment.

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days of oral glucocorticosteroids. This resulted in disappearance of her fever within 24 hours and virtually complete resolution of her rash within 4 days. Vemurafenib was then restarted at a 50% dose on day 23. On day 33, minimal asymptomatic erythema was seen on all 4 extremities. The large lesion at the prior left humeral surgical site was still somewhat erythematous, with mild skin induration over approximately a 3-cm area but without any other palpable abnormality (Figure 2). The large scapula lesion was 1 cm. The skin lesions on the chest and abdominal walls were less than 1 cm and the left posterior neck lesion was barely palpable. Most of the smaller skin lesions were no longer palpable. All of the patient's pain had resolved.

On day 47, the continued disappearance of smaller lesions and shrinkage of induration on the left humeral site were noted. The patient's rash had disappeared. The vemurafenib dosage was increased to 720 mg twice daily, and on day 50 was returned to full dosage.

Discussion

This case represents a truly rapid and remarkable response of MPNST to systemic therapy. To the authors' knowledge, this is unprecedented in the treatment of this disease and opens a new avenue to be explored in the search for better treatment for these unfortunate patients.

Much effort has recently been devoted to the study of the genome of MPNST. This has been



Figure 2 Day 33 of vemurafenib treatment.

characterized by the activation of the RAS pathway caused by the loss of tumor suppressor neurofibromatosis type 1 (NF-1) in approximately 40% of both familial and sporadic MPNST.^{1,2} The mutation of NF-1 results in the loss of neurofibromin, which normally downregulates RAS proteins. The increase in RAS activity increases the activation of multiple other pathways, including the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K/AKT) pathways, which stimulate cell growth.³ BRAF is an immediate downstream effector kinase of RAS in the MAPK pathway, and is therefore activated in these tumors. BRAF then phosphorylates MAPK kinase (MEK), which activates extracellular signal-regulated kinase (ERK), resulting in tumor growth.

Ambrosini et al⁴ studied these pathways in vitro in MPNST. They showed that sorafenib, which has been shown to inactivate BRAF, is an effective drug in this setting. Sorafenib was shown to reduce MEK activity, among other effects, resulting in tumor death. However, other studies have suggested that effective antitumor therapy with sorafenib may actually be mediated by mechanisms unrelated to BRAF inhibition.⁵ Clinically, Maki et al⁶ reported that 2 of 12 patients with MPNST had significant tumor regression with sorafenib treatment, although neither improvement met RECIST criteria for response, similar to the results seen in the present patient.

In addition to increased stimulation by RAS, BRAF activity may be increased by the activating *BRAF* V600E mutation, which has now been identified in several tumor types, including 40% of papillary thyroid cancers, 10% to 65% of astrocytomas, 80% of benign nodal nevi, 15% of colon cancers, up to 20% of schwannomas, approximately 50% of melanomas, and almost all cases of hairy cell leukemia.^{7–13} The success of antitumor therapy for melanoma using vemurafenib, an inhibitor of this mutated form of *BRAF*, has often been very dramatic.¹³ At the same time, the treatment of *BRAF*-mutated colon cancer and papillary thyroid cancer with this drug has been disappointing.^{12,14}

The *BRAF* V600E mutation is an uncommon event in MPNST, with a reported incidence ranging from 0% to 12.5%.^{1,2,8–10} The patient reported in the present study would therefore represent a minority of patients with MPNST, with an occurrence rate similar to the approximately 5% incidence of anaplastic

lymphoma kinase mutation in non-small cell lung cancer, in which crizotinib has had a major impact.¹⁵ The dramatic tumor response to vemurafenib and the modest effect of sorafenib reported here echo the results reported in the treatment of melanoma, and suggest that the BRAF V600E mutation is a dominant driver of cell growth in affected patients with MPNST. Patients with MPNST should be screened for BRAF V600E mutations and treated with BRAF inhibitors when these mutations are found, so that both the response rate and durability of response in this disease can be determined. Furthermore, because elevated BRAF activity may also be present in this disease by virtue of increased RAS activity resulting from the loss of NF-1-mediated production of neurofibromin,^{1,2} the possibility exists that inhibitors that block RAS, MEK, or ERK through other mechanisms might be useful in treating MPNST lacking the BRAF V600E mutation as a result of blocking the MAPK pathway at points other than BRAF. Jessen et al³ recently showed inhibition of human neurofibroma cell growth with an MEK inhibitor when human tumor cells were implanted into mice. Studies in patients with melanoma have shown resistance to vemurafenib as a result of activating mutations of NRAS and MEK, and encouraging trials have been completed combining vemurafenib with trametinib, an inhibitor of MEK, in the treatment of this disease.^{16–18}

Resistance to vemurafenib has been shown in BRAF-mutated colon cancer in vitro to be mediated by increased RAS activity produced by activation of both epidermal growth factor receptor (EGFR)¹⁹ and the PI3K/AKT pathway.²⁰ In the case of thyroid cancer, it has been shown that resistance to BRAF inhibitors can occur as a result of derepression of HER3 by inhibition of mutated BRAF, resulting in increased RAS activity.21 This rebound HER3 activity can be blocked in vitro with lapatinib.²¹ Increased EGFR activity has been reported in cell lines from patients with MPNST in vitro,²² and increased PI3K/AKT activity as the result of RAS activation has been shown in patients with MPNST, along with deregulation of mTOR.²³ These studies suggest additional potential targets for combined treatment with BRAF inhibitors. Finally, other BRAF inhibitors, such as dabrafenib, are now becoming available.²⁴ The hope is that they will be able to overcome the genetic resistance mechanisms being reported for BRAF itself with regard to vemurafenib.²⁵

Of particular interest, in light of this case, would be the evaluation of vemurafenib in *BRAF*-mutated schwannomas, which, although benign, can often be extremely debilitating when not surgically remediable. Should BRAF blockade prove to be useful in this tumor, it would also represent another indication that, although *BRAF* mutation is a strong driver of cell growth, additional genetic changes are required to produce metastatic growth. This dichotomy has already been noted in the case of benign nodal nevi, which often harbor *BRAF* mutations.^{11,26}

Conclusions

This report presents the first case of significant systemic antitumor activity in the treatment of MPNST with vemurafenib. Given the lack of effective systemic therapy for this disease, it is important to test all of these patients for the presence of *BRAF* mutations so that the effectiveness of treatment with BRAF inhibitors and related drugs can be further evaluated. Additional inquiry will hopefully result in an improved understanding of the biology and treatment of tumors harboring *BRAF* mutations, and a greater understanding of the mechanisms of both cell growth and metastatic spread. Furthermore, the success of vemurafenib will stimulate the search for other tumors in which *BRAF* mutations are important drivers of cell growth.

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Posttest Questions

- 1. True or False: The presence of a *BRAF* mutation in a tumor is an absolute indicator of malignancy.
- 2. Therapy directed against *BRAF* V600 mutation with vemurafenib has been successful in the treatment of which malignancy?
 - a. Papillary thyroid cancer
 - b. Melanoma
 - c. Colon cancer

 Resistance to V600-mutated BRAF inhibitors can occur by which of the following mechanisms?

- a. Further mutation in BRAF
- b. Derepression of HER3
- c. Activating mutations of NRAS and MEK
- d. All of the above

