Cotreatment of Hairy Cell Leukemia and Melanoma With the *BRAF* Inhibitor Dabrafenib

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Abstract

The activating *BRAF* mutation p.V600E has been identified in many cancers, including colon and lung adenocarcinomas, papillary thyroid cancer, malignant melanoma, and hairy cell leukemia (HCL). Malignant melanoma and HCL are of particular interest because of both the high proportion of cases harboring the mutation and the dramatic responses to *BRAF* inhibitor therapy reported in the literature. This report presents a patient with HCL and malignant melanoma with the *BRAF* p.V600E mutation, and discusses the successful treatment of both cancers with the *BRAF* inhibitor dabrafenib. (J Natl Compr Canc Netw 2015;13:9–13)

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Learning Objective

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

- Explain the potential benefit of utilizing a single *BRAF* inhibitor to treat a patient with multiple *BRAF*-mutated malignancies

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The recognition that some cancers can be driven by the presence of a single genetic lesion has helped usher in a new era of molecular diagnosis and treatment in oncology. Although this phenomenon was first recognized and therapeutically exploited in chronic myelogenous leukemia, a tremendous number of recent discoveries have identified the genetic underpinnings of many cancers and have led to the development of selective therapies to target these lesions. The relationship between genetic events and the resultant neoplasms are varied: some genes are commonly mutated in a wide variety of cancers (eg, *TP53* and *KRAS*) and others seem to be more specifically restricted to a particular malignant histology (eg, *NOTCH2* in marginal zone lymphoma).[1]

The *BRAF* p.V600E mutation has recently been identified in both solid and hematologic cancers, including adenocarcinoma of the colon, lung, and ovary (9%, 3%–5%, and up to 35%, respectively); papillary thyroid cancer (up to 69%); malignant melanoma (40%–60%); and hairy cell leukemia (HCL; up to 100% in a landmark paper).[2–9] Melanoma and HCL are of particular interest because both diseases have shown dramatic responses to therapy with the small molecule *BRAF* inhibitor vemurafenib.[7,10] The newer *BRAF* inhibitor dabrafenib has also been approved for use in melanoma.

This report presents the first case of the co-occurrence of malignant melanoma and HCL, both harboring the *BRAF* p.V600E mutation, and its successful treatment with the *BRAF* inhibitor dabrafenib.

Case Presentation

Hairy Cell Leukemia

A 67-year-old man with a medical history of diverticulosis, dyslipidemia, folliculitis, and mitral valve prolapse presented with excessive fatigue and cough. On screening blood work, leukocytosis was detected. Peripheral blood immunophenotyping revealed the presence of lambda restricted B-lymphocytes simultaneously expressing CD11c, CD19, CD20 (bright), CD25, CD103, and FMC-7. A bone marrow biopsy showed the marrow to be hypercellular (80%), with approximately 70% of the marrow cellularity consisting of lymphoid aggregates, with lymphocytes displaying a characteristic fried-egg appearance and reticulated cytoplasmic borders. Based on these results, a diagnosis of classical HCL was made. Treatment was initiated with cladribine, 0.12 mg/kg/d as a 2-hour intravenous infusion for 5 days, because his hemoglobin level was 10.7 g/dL and platelet count was 43×10^3/mcL. He then experienced a hematologic complete remission (CR).

Two years later, the patient became progressively more neutropenic and a bone marrow biopsy revealed recurrent disease. He was successfully treated again with cladribine at a dosage of 0.09 mg/kg/d via a 7-day continuous infusion and experienced a hematologic CR. This remission was more durable, but the patient experienced a relapse again almost 5 years later, with neutropenia and thrombocytopenia. He then received 12 doses of pentostatin, 4 mg/m^2 and achieved a hematologic CR. However, the results of his bone marrow biopsy showed small persistent disease (0.3% of lymphocytes, consistent with HCL). He was also found to have new dyserythropoiesis in his marrow and clinical neurologic toxicity; therefore, cytotoxic chemotherapy was discontinued. Partial remission was sustained for the following 2 years with suboptimal, but tolerable, hematologic parameters.

Malignant Melanoma

Two years after treatment with pentostatin, the patient developed an 8-mm red nodule on the extensor surface of his right forearm, and the results of a shave biopsy showed nodular melanoma. He subsequently underwent a wide excision and sentinel lymph node evaluation. Pathologic findings confirmed the diagnosis of melanoma with a depth of 4.05 mm, mitotic rate of 5/mm^2, no ulceration, no satellite lesions, and negative sentinel lymph nodes. Adjuvant sargramostim (granulocyte-macrophage colony-stimulating factor) was postoperatively administered for 12 months. Unfortunately, after this treatment period, a new satellite nodule developed proximal to the site of the prior excision. Results of PET/CT and MRI scans showed another deeper lesion medially in the midportion of the right arm (Figure 1). Notably, PET/CT also showed intense focal enhancements in the spleen. Excisional biopsy of the new superficial and deep lesions revealed locally recurrent melanoma, with the superficial lesion having a depth of 4.8 mm and a mitotic rate of 12/mm^2; the excised deeper lesion was approximately 1.8 cm in maximum diameter, was present in the subcutis, with a distance of

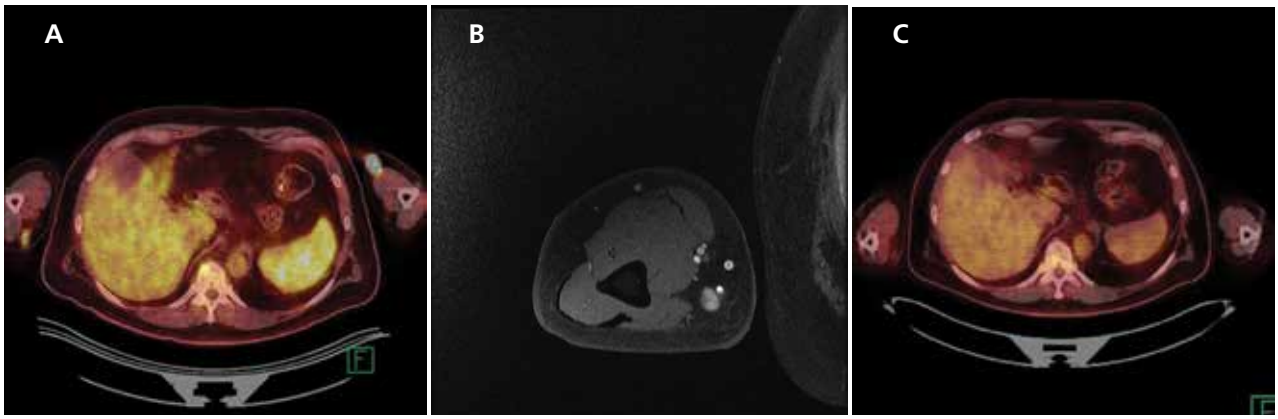

Figure 1 (A) PET/CT scan, (B) MRI of local melanoma recurrence, and (C) resolution of FDG avidity in arm and spleen.

0.8 mm to the nearest perpendicular resection margin and a mitotic rate of 18/mm^2. The excised lesion was sent for molecular testing and the patient then began a course of radiotherapy (30 Gy delivered over 14 days) to the affected limb.

At this time, the patient was also found to be thrombocytopenic (platelet count approximately 100×10^3/mcL) and had developed new splenomegaly on physical examination. In addition, the soluble interleukin-2 receptor (a marker of disease activity in HCL) was increasing (peak, 3952 U/mL; normal, <970 U/mL), and results of a bone marrow biopsy showed a 20% cellular marrow with 40% involvement by classical HCL (Table 1).

Treatment With Dabrafenib

Bone marrow aspirate and formalin-fixed paraffin-embedded tissue from the second melanoma resection were sent to the molecular diagnostics laboratory at The Ohio State University where *BRAF* mutation testing was performed. Briefly, in a Clinical Laboratory Improvement Amendments–certified procedure, the genomic DNA was amplified with custom in-house PCR primers, after which the DNA was sequenced using fluorescent capillary electrophoresis on an ABI PRISM Genetic Analyzer (Applied Biosystems, Carlsbad, CA). Presence of the p.V600E mutation was documented in the bone marrow aspirate and the melanoma. Because the mutation was present in his HCL cells, the patient was eligible for and enrolled on a phase I clinical trial of dabrafenib for *BRAF* p.V600E/K mutant malignancies (ClinicalTrials.gov identifier: NCT01340846), in which dabrafenib was initiated orally at a dosage of 150 mg, twice daily.

After three 28-day cycles, the bone marrow cellularity had improved to 30%, with a decrease in the leukemic content to 10% to 15% of marrow cellularity (Table 1). After 6 cycles, the bone marrow cellularity was normal for his age with no residual HCL detectable by immunohistochemical stains or flow cytometric immunophenotyping. PET/CT scan showed no fluorodeoxyglucose-avid lesions, with resolution of the previous upper extremity mass, resolution of focal splenic fluorodeoxyglucose avidity, and no splenomegaly. Currently, the patient is status post 18 cycles of therapy with dabrafenib without evidence of HCL or melanoma. To date, he has tolerated therapy well, with only the development of characteristic RAF inhibitor–associated skin changes[11] and one instance of squamous cell carcinoma that was excised. He will remain on therapy while he is deriving clinical benefit, per protocol.

Discussion

Activating mutations of *BRAF* are found overwhelmingly at codon 600 in the activation loop and are primarily a change from valine to glutamic acid, with a lysine substitution being the second most common, and mutations in other codons being found variously in visceral organ cancers.[12] The canonical p.V600E mutation permits signaling through downstream MAPK effectors independent of upstream activation by RAS, and is thought to be responsible for driving cancer cell proliferation, although whether the mutation itself is sufficient for oncogenic transformation is unclear. Although *BRAF* p.V600 mutations are present at variable levels in various cancers, HCL, melanoma, and papillary thyroid cancer have

Table 1 Hematologic Response to Treatment With Dabrafenib

	Pretreatment	After Cycle 3	After Cycle 6
WBC, x 103/mcL	2.7	4.7	5.9
Hemoglobin, g/dL	14.3	14.7	15.6
Platelets, x 103/mcL	161	149	186
Bone marrow			
Cellularity	20%	30%	50%
Hairy cell leukemia	40%	10%–15%	0%

shown high rates of mutation, with HCL and melanoma of particular note for having demonstrated dramatic responses to BRAF inhibition. The question then arises regarding how to treat individuals with more than 1 malignancy and the *BRAF* mutation. The patient in this report experienced a CR in HCL after 6 cycles of dabrafenib, although his time to response was slower than that reported by Dietrich et al.[10] Anticipated survival for resected locally recurrent melanoma is 12 months.[13] The present patient is now 23 months from his first melanoma recurrence, with no evidence of melanoma. The impact of BRAF inhibitors as adjuvant therapy for melanoma is unknown and currently being studied in phase III trials (ClinicalTrials.gov identifiers: NCT01667419, NCT01682083).

Notably, HCL and melanoma have also been subdivided into groups in which the *BRAF* mutation is either enriched or uncommon. In particular, although HCL was initially reported to have a *BRAF* mutation rate of up to 100%, additional studies have shown that HCL with particular *IGHV@* gene use has a near zero rate of *BRAF* mutation.[14] Similarly, although nodular (the histologic subtype present in this case) and superficial spreading melanomas are enriched for *BRAF* mutations, the mutation is virtually absent in uveal melanoma.[8]

Recently, investigators have demonstrated that the *BRAF* mutation is present in hematopoietic stem cells (HSC) of patients with HCL.[15] Further, induction of mutant *BRAF* in mature B cells in mice has been shown to not give rise to the HCL phenotype, suggesting that the pathologic mutation arises early in hematopoietic or lymphoid development. In addition, a germline *BRAF* p.V600G mutation has been described in a patient with cardiofaciocutaneous syndrome, suggesting that germline *BRAF* mutation is compatible with human growth and development.[16]

In an effort to determine if the present patient had a germline, common lymphoid progenitor, or HSC *BRAF* mutation, peripheral blood was collected with patient consent under an Institutional Review Board–approved protocol. T cells were isolated and results confirmed the absence of HCL through flow cytometry (96% of events were CD3+, although 1.1% were CD3+, CD16+, and CD56+; 1.1% were CD3–, CD16+, CD56+; and no events were CD19+). Genomic DNA was extracted from the T cells, and DNA surrounding the *BRAF* 600 codon was amplified and sequenced using Sanger methodology. No evidence existed of a *BRAF* p.V600 mutation in the T-cell DNA. These results suggest that the *BRAF* mutation arose independently in the melanoma and HCL, but did not exclude the possibility of either chimerism or pluripotent stem cells giving rise to both HSC and neural crest cells. Further investigation is needed to better understand multiple neoplasms within patients who present with common genetic lesions.

Conclusions

This case report documents the co-occurrence of 2 *BRAF* mutant cancers and the successful treatment of both with one molecularly targeted therapy. Because of the increased risk of a secondary primary malignancy in patients with HCL, patients with *BRAF*-mutated HCL who develop a second primary malignancy should be considered for *BRAF* mutation testing of solid tumors, because cotreatment may be possible. As more is learned about the molecular underpinnings of cancer, it remains to be seen how often we will discover common mechanisms at work in synchronous or metachronous cancers within individual patients.

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Instructions for Completion

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Posttest Questions

1. True or False: Dabrafenib is an MEK inhibitor.
2. Which of the following are the 2 most common *BRAF* mutations at codon 600?
   a. Valine to glycine; valine to leucine
   b. Leucine to lysine; leucine to glycine
   c. Valine to lysine; valine to glutamic acid
   d. Cysteine to glutamic acid; cysteine to lysine
3. Which of the following diseases is not characteristically *BRAF*-mutated? There is only one correct answer.
   a. HCL
   b. Uveal melanoma
   c. Papillary thyroid cancer
   d. Nodular melanoma