KRAS G12V Mutation in Acquired Resistance to Combined BRAF and MEK Inhibition in Papillary Thyroid Cancer

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ABSTRACT

BRAF V600E mutations occur in approximately 40% of all patients with papillary thyroid cancer (PTC) and are associated with a worse prognosis in population studies. Treatment with single-agent BRAF inhibitors can result in nondurable partial responses (PRs) in clinical trials, but resistance inevitably develops. The mechanisms of resistance are not completely understood, but in non-thyroid tumors harboring *BRAF* V600E mutations, resistance has been ascribed to concurrent or acquired mutations in *MEK1/2, RAC1, KRAS,* and *NRAS.* This case report describes a patient with radioactive iodine–refractory metastatic PTC treated in a clinical trial with combination BRAF and MEK inhibition who achieved a durable PR. At time of progression, biopsy revealed an acquired *KRAS* G12V–activating mutation. The patient subsequently went on to have a PR to cabozantinib therapy in the clinical trial. This is the first reported case of an acquired *KRAS*-activating mutation that developed during treatment with BRAF and MEK inhibition in a patient with *BRAF*-mutated PTC. The *KRAS* mutation was also detected in peripheral blood samples taken as part of the trial, indicating that resistant mutations may be identified through noninvasive means. The identification of resistant mutations in patients at time of progression is necessary to identify possible therapeutic options including potential clinical trials.
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Over the past several years, clinical trials have led to FDA approval of the multikinase inhibitors (MKI) lenvatinib (February 2015)[1] and sorafenib (November 2013)[2] for treatment of radioactive iodine (RAI)–refractory, progressive, differentiated thyroid cancer (DTC). Yet, for both of these MKIs, acquired resistance is universal, adverse events are common, and no overall survival benefit has been demonstrated. Papillary thyroid cancer (PTC) is primarily driven by constitutive activation of the RAS/RAF/MEK/ERK pathway, a key oncogenic signaling cascade for many human malignancies.[3] Activating *BRAF* mutations are the most common cause for this activation in PTC, occurring in 25% to 49% of tumors. Moreover, the presence of this mutation is associated with more advanced disease and poorer prognosis.[4–6] Although there are currently no approved BRAF-targeted treatments for patients with PTC, a phase II trial of the BRAF inhibitor vemurafenib in patients with RAI-refractory, *BRAF*-mutated PTC demonstrated a response rate of 35%.[7] Resistance to BRAF inhibition is likely to develop eventually, which has been demonstrated in melanoma, and is thought to occur through reactivation of the MAPK pathway.[8]

Combination dabrafenib/trametinib is now the standard therapy for patients with melanoma harboring *BRAF* V600E mutations based on increased response rates and overall survival.[9] However, resistance to dual inhibition eventually develops in most patients due to somatic mutations in *MEK1/2*, *KRAS*, or *NRAS*, and amplification of the *BRAF* V600E mutant alleles.[10–13] Mechanisms of resistance to combination BRAF and MEK inhibition remain to be fully elucidated in PTC. Danysh et al[14] reported in vitro studies wherein a *BRAF* V600E–mutated thyroid cancer cell line selected for resistance to vemurafenib developed an acquired novel *KRAS* G12D–activating mutation. Cabanillas et al[15] reported a case of a patient with anaplastic thyroid carcinoma treated with dabrafenib/trametinib in whom an

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NRAS Q61K mutation was discovered on tumor tissue after 4 weeks of treatment. The present case report describes for the first time the development of an activating *KRAS* G12V mutation as a potential resistance mechanism in a patient with PTC treated with combination dabrafenib/trametinib who experienced a subsequent response to cabozantinib.

Case Report

A 67-year-old woman diagnosed with PTC underwent total thyroidectomy with central neck dissection, which revealed a 7.2-cm extensive right lobar, poorly differentiated PTC with 3 of 9 lymph nodes positive and a background of Hashimoto thyroiditis. Following surgical resection, imaging revealed bilateral pulmonary nodules and mediastinal adenopathy. She received 100.9 mCi of RAI therapy, and a posttreatment scan showed uptake in the thyroid bed but none in the chest. The tumor was staged as a pT3pN1aM0 poorly DTC. Repeat imaging 6 months after initial diagnosis and treatment revealed increasing adenopathy in the neck and bilateral subcentimeter pulmonary nodules, and the patient underwent right radical neck dissection with 4 of 52 examined lymph nodes positive for PTC, with no extranodal extension noted. Six months later, imaging again revealed an enlarged right paratracheal node and anterior paratracheal node, which were resected and determined to be positive for PTC. The patient went on to receive external-beam radiotherapy to the neck at an outside institution. She was then started on sorafenib, 400 mg twice daily, which initially was poorly tolerated and she developed hand-foot syndrome and diarrhea. With the aid of supportive measures and minimal dose interruption, she was able to remain on sorafenib at 400 mg twice daily for 2 years with stable disease as the best response (supplemental eFigure 1, available with this article at JNCCN.org).

After experiencing progressive disease, the patient was enrolled in a clinical trial and started on lenvatinib (ClinicalTrials.gov identifier: NCT01321554).[1] She remained on lenvatinib, 24 mg daily, for 6 months before experiencing progressive disease in both the neck and chest. Her treatment course was complicated by hypertension, hand-foot syndrome, hypercalcemia, and proteinuria, requiring dose interruptions and reductions. Her tissue from previously resected metastatic lymph nodes was assessed by PCR for the presence of a *BRAF* mutation and found to be positive for *BRAF* V600E. She was then enrolled in another clinical trial (NCT01723202) and randomly assigned to combination therapy with dabrafenib, 150 mg twice daily, and trametinib, 2 mg daily. After 2 cycles, she sustained a partial response (PR) in the thyroid bed, cervical and intrathoracic lymph nodes, and pulmonary lesions, with a RECIST v1.1 decrease of 67% in the target lesions, including a dramatic decrease in the size of the thyroid bed tumor from 6.1 to 2.3 cm (Figure 1). Thyroglobulin levels initially increased from 1,601 ng/mL at baseline to 3,620 ng/mL after 2 months of therapy, before decreasing steadily to a nadir of 385 ng/mL at the time of disease progression. The patient's treatment course was complicated by rash and fevers, which required low doses of prednisone and reduced doses of dabrafenib (100 mg orally twice daily) and trametinib (1.5 mg daily). She also experienced an episode of cholecystitis that was treated with cholecystectomy after 8 cycles, but otherwise experienced minimal toxicities.

The patient was maintained on combination therapy for 18 months before discontinuing the trial due to progressive disease. A biopsy was obtained at progression and whole-exome sequencing was performed on the biopsy tissue, her germline DNA, and DNA purified from the archival primary tumor (eAppendix 1). *BRAF* V600E mutation was verified in both the archival and progression tumor biopsies, in addition to 24 other deleterious mutations found in the original tumor. Mutations detected at progression were cross-referenced against Condel, SIFT, PolyPhen, and PROVEAN and were considered a candidate if they were identified as deleterious or damaging on at least 3 of the 4 platforms (supplemental eTables 1–3). Of these mutations, the *KRAS* G12V mutation was most likely the driver of resistance to therapy. In addition, blood-based digital droplet PCR (ddPCR) was performed as part of the clinical study (eAppendix 1), which demonstrated both a rapid decline in *BRAF* V600E copies after therapy initiation and a re-emergence of *BRAF* V600E in addition to *KRAS* G12V at clinical progression (Figure 2). Both *BRAF* and *KRAS* ddPCR were detectable 2 cycles before treatment discontinuation due to clinical progression. The patient subsequently received cabozantinib therapy on a clinical trial (ClinicalTrials.gov identifier: NCT01811212) and experienced a PR, with a 45% reduction in target lesions. She continued on therapy for 9 months at a reduced dose due to hand-foot syndrome and hyponatremia, before experiencing a decline in performance status and progressive disease, and died soon thereafter.

Discussion

Thyroid cancer is the most common form of endocrine malignancy worldwide, and DTC is the most common histologic subtype, which includes papillary, follicular, and Hürthle cell histologies. Treatment is typically surgery, and in select cases is followed by RAI and thyroid-stimulating hormone suppression therapy. For patients who develop metastatic RAI-refractory disease, treatment options are limited. Recently, the 2 MKIs sorafenib and levatinib were FDA-approved for this population based on large phase III trials, yet neither have demonstrated

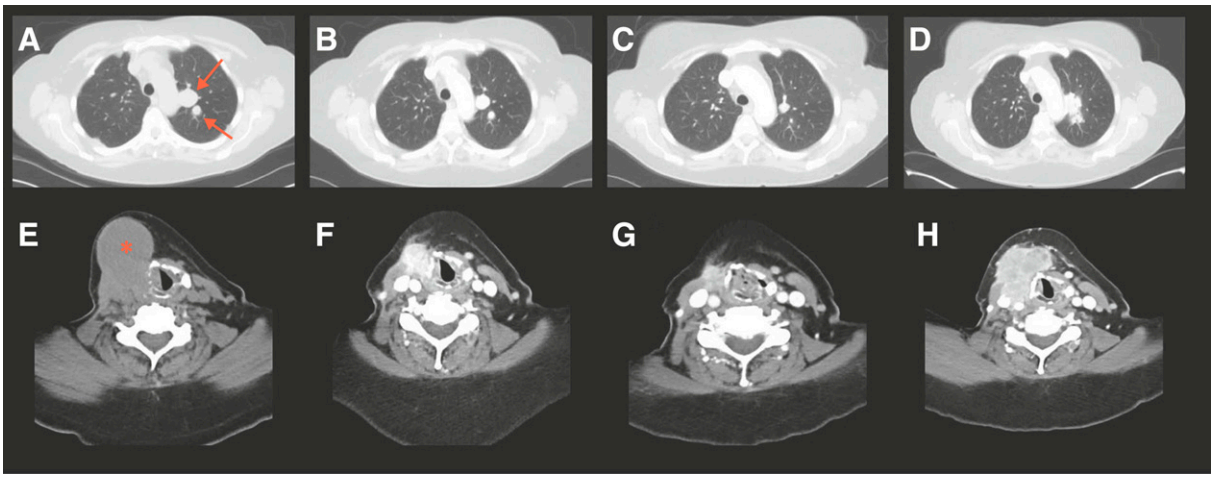

Figure 1. Clinical response to combined BRAF and MEK inhibition. Representative images are from chest CT (A–D) and neck CT (E–H) of the target lesions in the left upper lobe (arrows) and right thyroid bed (asterisk) at baseline (A, E), after 2 cycles (B, F), after 10 cycles (C, G), and at progressive disease after 20 cycles (D, H).

complete remission or improved survival.[1,2] As our aforementioned experience demonstrates, these medications are associated with significant toxicities, including hypertension, hand-foot syndrome, fatigue, nausea, diarrhea, bleeding, thrombosis, and cardiac arrhythmias.[16] Oncogenic mutations in *BRAF* V600E occur in roughly half of patients with PTC and are associated with poor prognosis.[6] We and others[17] have demonstrated that clinical trial populations are enriched for patients with this mutation. Clinical trials are ongoing with BRAF inhibitors, including a recently completed phase II trial of vemurafenib in 51 patients, which demonstrated an overall response rate of 35%.[7] Based on studies in patients with melanoma in which combined BRAF and MEK inhibition was observed to improve response and survival,[18] a clinical trial of dabrafenib alone or in combination with trametinib in patients with RAI-refractory, *BRAF*-mutated thyroid cancer is underway (ClinicalTrials.gov identifier: NCT01723202). Furthermore, preclinical and clinical studies of BRAF and/or MEK inhibitors in early-stage, RAI-refractory DTC show promising new avenues for treatment of these patients; this is based on the ability of BRAF and/or MEK inhibitors to stimulate RAI uptake, thereby regaining iodine avidity that can be targeted by RAI. Such therapy may be more suitable for patients with low tumor burden and indolent disease before FDA-approved MKIs are considered.[19–22]

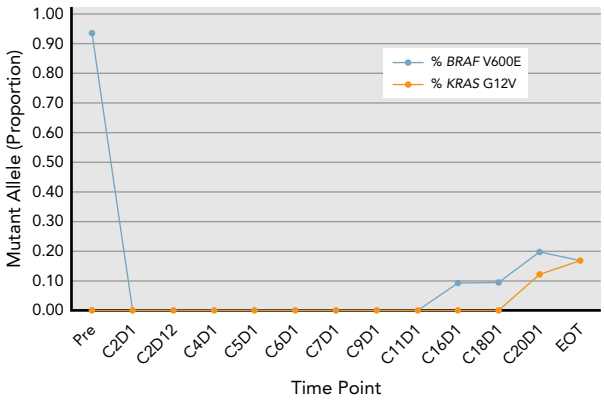

Figure 2. Blood-based monitoring of *BRAF* V600E and *KRAS* G12V mutations demonstrate possible emergence of resistance that corresponded to clinical disease progression.
Abbreviation: EOT, end of treatment.

As with other targeted agents, resistance eventually develops in patients treated with combination BRAF and MEK inhibitors. Previously described mechanisms of resistance to BRAF inhibition in thyroid cancer have been focused on primary resistance and included alternate *BRAF* splicing,[23] c-MET–mediated reactivation of the PI3K/AKT pathway,[24] and copy number gain of MCL1 and loss of CDKN2A.[25] Potential resistance mechanisms to BRAF and/or MEK inhibition, described in other solid tumors, include mutations in *MEK1/2*, *RAC1*, *KRAS*, or *NRAS*, and amplification of the *BRAF* V600E mutant alleles.[11,12] *KRAS*, *ARAF*, and *MEK1*-resistance mutations have been described in patients with *BRAF*-mutated colon cancer treated with combination dabrafenib/trametinib.[10,13] Recently, a study found that prolonged treatment of thyroid cancer cell lines with vemurafenib led to the development of a *KRAS* G12D mutation, which the investigators proposed may confer resistance by sustaining RAS/MEK/ERK signaling and PI3K/AKT pathway activation through EGFR and HER3.[14] Importantly, although these cells were resistant to vemurafenib monotherapy, combination treatment of vemurafenib and PI3K and ERK1/2 inhibitors remained active, whereas BRAF

and MEK inhibition did not. This is further supported by the recent report of an *NRAS* Q61K mutation seen in a patient with anaplastic thyroid cancer after 4 weeks of treatment with combination BRAF and MEK inhibition.[15]

By the time our patient began BRAF and MEK combination therapy, she had exhausted all standard options for PTC, including surgical resection, RAI, external-beam radiotherapy, and both FDA-approved MKIs sorafenib and lenvatinib. She had significant tumor burden in her neck, chest, and bones. Despite this, she experienced a sustained PR to treatment with BRAF and MEK inhibition for 18 months with improvement in her tumor burden. Our patient's trend in serum thyroglobulin levels is also of high interest, with an initial uptrend despite PR and levels decreasing to nadir at progression. This is possibly secondary to tumor redifferentiation that can be seen with BRAF inhibitor therapy.[19,26,27] The finding of a *KRAS* G12V mutation supports the preclinical models of resistance to single-agent BRAF inhibition in thyroid cancer and combination BRAF and MEK inhibition in both melanoma and colon cancer.[10,13,14] For example, preclinical studies in colorectal cancer have revealed that *KRAS* mutations in G12D and G13D led to resistance to combined BRAF and MEK inhibition, and in a clinical study of dabrafenib, trametinib, and panitumumab in patients with *BRAF*-mutated colon cancer, *KRAS* or *NRAS* mutations were detected at the time of disease progression but not at baseline.[10,13] A second preclinical study of colorectal cancer found acquired *KRAS* mutations in exons 2 and 4 (G12D, G13D, and A146T/V) to combination therapies with BRAF and EGFR inhibition or combination BRAF, EGFR, and PI3K-α inhibitors, while the same authors reported the emergence of an acquired mutation in *KRAS* G12C in a patient with colorectal cancer treated with combination BRAF and MEK inhibition in a clinical trial.[28] In melanoma, mutations in *NRAS* and *KRAS* have been reported in patients who developed resistance to BRAF inhibitors, but *NRAS* mutations were far more common (17% vs 2%), and specific allelic mutations were not reported.[29]

A limitation of our study is that the archival tumor specimen was obtained at the time of surgical reresection before treatment with external-beam radiotherapy, sorafenib, and lenvatinib. Ideally, both tissue and cell-free DNA would be evaluated at baseline before BRAF and MEK inhibition to ensure that the *KRAS* mutation did not develop as a result of prior treatment, although the absence of *KRAS* on cell-free DNA at baseline is reassuring. Further research is needed to confirm this resistance mechanism, and to develop strategies to both prevent resistance and prolong clinical responses, such as combination therapy with downstream ERK inhibitors. In preclinical models, MEK-resistant cell lines retained sensitivity to selective ERK1/2 inhibition in colorectal cell lines.[30] Clinical trials with ERK inhibitors are ongoing with dose escalation in both a single-agent (ClinicalTrials.gov identifier: NCT01781429) and in combination with chemotherapy (NCT02608229). Our patient's subsequent response to cabozantinib indicates the importance of identifying the optimal sequencing strategy for patients who develop resistance to targeted therapy. In a subset analysis of a phase III trial of cabozantinib in medullary thyroid cancer, patients with *RAS* mutations seemed to derive clinical benefit in terms of response rates and progression-free survival.[31] The mechanism through which cabozantinib may exert its effect on *RAS*-mutated tumors remains unclear, but preclinical models suggest that MET signaling may be essential for *KRAS*-mediated, anchorage-independent cell growth.[32] MET inhibition by cabozantinib may impact downstream ERK and AKT and may therefore have contributed to the clinical response seen in our patient. Finally, the clinical responses observed by Iyer et al[33] in patients with resistant anaplastic thyroid cancer treated with pembrolizumab and targeted therapy indicates the possible role of checkpoint inhibitors in this setting.

Conclusions

This report presents a patient with *BRAF*-mutated PTC who initially sustained an excellent response to treatment with BRAF and MEK inhibition but was found to have developed a *KRAS* G12V mutation at time of progression that may be a secondary resistance mechanism. This observation is further supported by data from peripheral blood ddPCR showing a decline in *BRAF* V600E detection during treatment, followed by the redetection of both *BRAF* V600E and *KRAS* G12V mutations at the time of clinical progression. Further research, including prospective clinical trials, should include assessment of *BRAF* V600E at the time of disease progression both within the tumor and from blood-based assays. Finally, strategies to prevent the development of resistance should be explored. For instance, our patient's subsequent response to cabozantinib may implicate AKT and ERK as viable therapeutic targets, as suggested in preclinical studies. In addition, combination or sequential treatment with immune checkpoint inhibitors may abrogate the development of resistance.

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