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LETTER TO THE EDITOR

Sweeping KRAS generalizations: are we depriving patients of an effective treatment? A novel KRAS mutation and dramatic response to panitumumab in a patient with metastatic colorectal cancer

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Dear Editor:
Is it accurate to generalize the predictive value of reported KRAS mutations to unreported KRAS codons? In our search to find biomarkers of EGFR inhibitor responsiveness, are we excluding patients that would benefit from treatment?

Insights into the molecular biology of colorectal cancer (CRC) and recent developments in gene sequencing and molecular diagnostics have led to the identification of biomarkers that can predict responsiveness to treatment. Molecular markers can identify patients who would most likely benefit from treatment and offer tailored therapy regimens.

Nowhere is the utility of predictive biomarkers more evident than determining the utility of EGFR inhibitors for the treatment of CRC. Biomarkers, such as KRAS and BRAF V600E mutations, have been found to predict resistance to EGFR inhibitors. Two EGFR inhibitors, cetuximab and panitumumab, have been approved by the Food and Drug Administration for treating CRC in KRAS and BRAF wild-type (WT) patients.

A sizeable body of literature demonstrates that KRAS mutations, and mutations in its downstream effector BRAF, are refractory to EFGR inhibitors. Various studies in CRC have determined that KRAS codon 12, 13, 61, and 146 mutations are predictive of resistance to treatment with anti-EGFR treatment in colorectal cancer. Consequently, the National Comprehensive Cancer Network and the American Society of Clinical Oncology recommend determination of KRAS mutation status in all patients with CRC who are candidates for EGFR inhibitors.

We present a case of refractory metastatic colorectal carcinoma with a novel KRAS mutation in codon 14 who had a dramatic response to panitumumab on radiographic imaging.

Our patient was a 72-year-old man who initially presented with constipation, underwent colonoscopy, and was diagnosed with adenocarcinoma of the sigmoid colon in October 2007. Rectosigmoid resection of the mass revealed a moderately differentiated adenocarcinoma with tumor invasion into serosa and perirectal soft tissue with vascular and perineural invasion. Surgical margins were negative, and eight lymph nodes were positive for adenocarcinoma (pT4pN2). Staging computed tomography (CT) at diagnosis found a solitary 5-cm liver mass.

In December 2007, he began adjuvant FLOX (5-fluorouracil/leucovorin/oxaliplatin) plus bevacizumab). After three cycles of FLOX, he developed grade IV diarrhea and significant weight loss requiring regimen suspension. In April 2008, he underwent right partial hepatectomy that confirmed metastatic adenocarcinoma consistent with colonic primary. In May 2008, a new enhancing mass was found in the left liver concerning new metastasis. He was

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started on FOLFIRI (fluorouracil/leucovorin/irinotecan) with bevacizumab, but subsequently changed to irinotecan with bevacizumab due to toxicity. In May 2009, he had radiographic progression of disease with increasing liver involvement. His therapy was then changed to capecitabine with bevacizumab and subsequently FLOX (bevacizumab/5-fluorouracil/leucovorin/oxaliplatin). In September 2009, his disease continued to progress, and he presented to us for further therapy. KRAS genotyping using polymerase chain reaction (PCR) with exon 1 flanking primers followed by single-strand conformational polymorphism (SSCP) analysis revealed band shifts compatible with an ATA mutation in codon 14 of exon 2. No mutations in codons 12 and 13 were found. Since the patient has received all the active agents and a novel mutation was found, further workup was warranted to decide about further therapy, particularly keeping in mind that the patient has excellent performance status (ECOG PS 0).

Therefore, further testing was performed which included BRAF gene, EGFR immuno-histostaining, and EGFR mutations. BRAF gene V600E mutation and EGFR mutation were not identified on PCR-SSCP. EGFR was +1 on immunostaining. The patient was consented and monotherapy with panitumumab (Vectibix) was initiated in April 2010 at a standard dose of 6 mg/kg (i.v.) every 2 weeks.

While on panitumumab he experienced grade 3 skin toxicity after two doses, requiring 50% dose attenuation (3 mg/kg) and change in administration at 3-week intervals. CT of chest, abdomen, and pelvis with contrast scan after four doses of panitumumab found an interval decrease in hepatic metastases (decreased from 4.3 to 3.1 cm), stable sigmoid mass extending to the left pelvic stable lung mass, and decreased mesenteric lymphadenopathy from 5.4 to 3.8 cm.

In summary, our patient with refractory metastatic colorectal carcinoma with a KRAS mutation in codon 14 had an extraordinary response to panitumumab on radiographic imaging. He was KRAS codon 12 and 13, BRAF V600E, and EGFR WT. Clinically, our patient experienced severe grade 3 skin toxicity that is associated with improved CRC symptoms, longer overall survival, and performance-free survival among panitumumab-treated patients.

This case is interesting on two fronts. First, it is the first case of a KRAS mutation in codon 14 reported for CRC. Secondly, unlike previously reported mutations in codons 12, 13, 61, and 146, this mutation in exon 14 did not predict responsiveness to anti-EGFR treatment. This highlights the point that it may not be accurate to generalize the predictive value of reported KRAS mutations to unreported KRAS codons. Since this is only a single case, exon 14 mutation's influence on clinical outcome and tumor characteristics requires further investigation.

The KRAS mutation identified in codon 14 results in a non-conservative valine to arginine amino acid substitution in the protein. It is unclear whether or not this mutation is activating. However, its abundance in tumor tissue implies that cells bearing this mutation appear to have a survival or proliferative advantage, suggesting that it is an activation mutation. Notably, normal tissue adjacent to the tumor was analyzed and the mutation in codon 14 was absent, indicating that the base change detected is an acquired somatic mutation rather than an inherited polymorphism.

In conclusion, generalizing the predictive value of previously reported KRAS mutations to other codons without evidence may deprive patients of an effective treatment. In our search to find biomarkers of EGFR inhibitor responsiveness, we may exclude patients that would benefit from treatment. The predictive value of unreported KRAS mutations to anti-EGFR therapies requires further investigation.