Why a One Size Fits All Approach to RAS Might Not Fit Colorectal Cancer

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Since the discovery that KRAS exon 2 mutations predict a lack of benefit from anti-epidermal growth factor receptor (EGFR) therapy in metastatic colorectal cancer, our understanding of RAS mutations has expanded considerably. Guidelines now suggest extended RAS characterization, which includes assessment of KRAS and NRAS for mutations at exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146). Extended RAS mutations appear to confer resistance to anti-EGFR therapy. With their inclusion, approximately 56% of patients will be defined as having a RAS mutation and will not be eligible for anti-EGFR therapy. In addition, atypical RAS mutations exist that are of unclear significance and difficult to study in any prospective manner given their rarity. Even within guideline-described codons there are mutations, such as KRAS A59T, that are of unclear significance. Studying these mutations individually would be nearly impossible, and they highlight a pressing issue of how we deal with variants of unknown significance (VUS). The number of uncommon VUS is likely to expand exponentially as clinical sequencing moves to more comprehensive sequencing platforms, and we will need solutions to deal with these variants.

In this issue of JNCCN, Lou et al (“Therapeutic Response of Metastatic Colorectal CancerHarboring a KRAS Missense Mutation After Combination Chemotherapy With the EGFRInhibitor Panitumumab”) present the case of a 50-year-old woman with a KRAS A59T–mutated metastatic colon cancer who received 4 cycles of FOLFIRI plus panitumumab and showed a radiographic partial response accompanied by a decline in carcinoembryonic antigen. The patient subsequently experienced disease control lasting 8 months while receiving FOLFIRI plus panitumumab. She was noted to have a KRAS A59T mutation after the treating institution changed from a Sanger sequencing platform specific to KRAS exon 2 to a more comprehensive amplicon-based next-generation sequencing (NGS) panel that included extended RAS coverage. The NGS panel was performed on DNA extracted from the same biopsy of the primary tumor as the Sanger sequencing. The authors propose that patients with KRAS A59T mutations may represent a population with continued sensitivity to anti-EGFR therapy.

Challenges and Opportunities in Studying Rare Biomarkers

Given the infrequency of many extended RAS mutations, they have not been well described individually and were considered as a group of mutations in the studies that support extended RAS mutation testing. Codon 59 mutations are particularly lacking in evidence to support their role in predicting resistance to anti-EGFR therapy. Only 7 patients with codon 59 mutations were described in the landmark PRIME trial analysis of extended RAS mutations, and these mutations were not part of the extended RAS mutation analysis. The evidence to support these mutations as a predictive marker was only the fact that removing these patients from the population with wild-type RAS resulted in a hazard ratio that made anti-EGFR agents appear more beneficial in wild-type patients. Clearly, further characterization of these variants is required, but how do we characterize them in a meaningful way? Using in vitro assays is one option. At our institution, the Precision Oncology Decision Support Team has a functional genomics assay using BaF3 and MCF10A cell viability studies to help characterize unknown
In the reported case, a partial response was noted in the pulmonary cancer patients. Distinct subsets of colorectal therapeutics for molecularly and the development of novel interest include the biology of colorectal cancer. His research enrichment program for study, a novel biomarker Colorectal Cancer (ATTACC) of Targeted Therapies Against for several phase I and II clinical he is the principal investigator of the NIH Gastrointestinal cooperative group, and a member of the NSABP/RTOG clinical oncology Steering Committee. He is the principal investigator for several phase I and II clinical trials, including assessment of Targeted Therapies Against Colorectal Cancer (ATTACC) study, a novel biomarker enrichment program for colorectal cancer. His research interests include the biology of the refractory colorectal cancer and the development of novel therapeutic for molecularly distinct subsets of colorectal cancer patients. Scott Kopetz, MD, PhD
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Is KRAS A59T Truly Sensitive to Anti-EGFR Therapy?

Although reports of patients with exceptional response can provide insight into the biology underlying response, application to clinical decision-making needs to be tempered. When we see reports of a single patient with a genomic biomarker experiencing an exceptional outcome, we must always consider whether a sequencing error could be present. Tumor heterogeneity is another important consideration not mentioned by the authors that should be considered when targeted therapies result in unexpected outcomes. Concordance between primary tumor and liver metastases RAS status appears high in colorectal cancer, ranging from 90% to 100%; however, discordance of up to 32% has been reported between lung or lymph node metastases and primary tumors. The fact that these alterations arose under selective pressure and coincide with clinical progression strongly argues that they predict resistance to anti-EGFR therapies and supports extended RAS mutations as predictive biomarkers. Unfortunately, KRAS codon 59 mutations have not been described as a mechanism of resistance in colorectal cancer to help guide our assessment of the current case.
A major barrier to understanding clonal dynamics is that we cannot truly know the genotype of every cell within a patient at all times. Possibly, patients with only part of their total tumor mass containing a RAS mutation may still derive benefit from anti-EGFR therapy. In the CRYSTAL trial, low allele frequency RAS mutations identified using highly sensitive bead emulsion PCR were shown to predict a lack of benefit in overall survival from anti-EGFR therapy. However, objective response rates appeared to show trends toward benefit in the low mutant allele frequency group. The strength of this trend continuously increased as the mutant allele proportion decreased. In the current report, we lack information about the mutant allele frequency and the mutation status of the metastases that responded to therapy, and this may be an important driver of response.

Conclusions

In the right context, KRAS A59T mutations may be sensitive to anti-EGFR agents. Does this case report prove it? No. It raises an important question about whether all RAS mutations are created equally and highlights the difficulties in characterizing uncommon variants. Although in vitro assays and real-world evidence may help us understand the significance of these variants, they are not definitive. A recent review of the literature and internal databases at our institution noted 98 unique RAS variants, many of which lacked characterization. We will never be able to fully define the significance of all of these mutations with prospectively collected data, and some degree of uncertainty will always remain. However, guidelines are built on best available evidence, and it will require more than case reports to justify a change.

References