Perspective

The heterogeneity of KRAS mutations in colorectal cancer and its biomarker implications: an ever-evolving story

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There was a frisson of expectation in 2008 when multiple retrospective studies all similarly concluded that patients whose colorectal (CRC) cancers harbored a KRAS mutation did not demonstrate benefit from monoclonal anti-epidermal growth factor (EGFR) antibodies; finally personalized medicine was entering the field of CRC therapy. Up to that point monoclonal anti-EGFR therapy had become standard-of-care for patients with refractory CRC, although radiographic responses observed with monotherpy were seen in less than 10% (1). EGFR expression by immunochemistry, assumed to be a relevant biomarker, was determined not to be predictive of efficacy (2). Although it was a negative biomarker (predictive of lack of efficacy) it made a major impact; the European Medicines Agency (EMEA) approval of panitumumab (3) and the Food and Drug Administration (FDA) changed in approval indication for cetuximab and panitumumab (4), restricted use of these agents in patient's whose tumors were KRAS wild-type. Biomarker assessment for patients with CRC rapidly became the practiced and routine standard-of-care.

Molecular assessment for KRAS mutation identification initially seemed relatively straight forward; the result was a binary and the probability of a false positive or false negative result was relatively low. However the significant molecular heterogeneity of CRC mutations appears to color the initial clear evidence (albeit retrospective) showing patients with advanced CRC failing to benefit from anti-EGFR therapy. The study by Tejpar *et al.* (5) is a large retrospective study of 1,378 patients who were enrolled onto the CRYSTAL and OPUS prospective randomized trials for whom KRAS mutation status was known. Their data confirmed prior observation (6) that for patients with CRC KRAS codon 12 tumors (either G12D or G12V) there was no benefit from the addition of the chimeric anti-EGFR inhibitor cetuximab to chemotherapy, in terms of radiographic response rate (RR), progression-free survival (PFS), nor overall survival (OS). However patients, whose tumors harbored a KRAS codon 13 mutation (G13D), had a statistically significant higher RR, PFS, but not an improved OS, when cetuximab was added to chemotherapy, or administered as monotherapy (when compared to best supportive care) (6). Two independent meta-analyses of published clinical trials support the observation that patients with G13D KRAS mutation treated with anti-EGFR therapy appear to have a superior RR, PFS, and OS when compared to patients with other KRAS mutant tumors (7,8). These observations have been subsequently supported by preclinical studies; seven human CRC cell lines with a codon 13 mutation were demonstrated *in vitro* to be sensitive to cetuximab therapy (9).

Does this indicate distinct tumor biology for KRAS G13D mutant CRC patients? Clinical studies suggest KRAS codon 13 patients may have superior outcomes with chemotherapy alone, without monoclonal anti-EGFR antibodies (10). Although the prognostic impact of a patient having a KRAS mutant tumor remains controversial, and is difficult to assess without the confounding impact of cancer therapy, it does appear that KRAS codon 13 tumors have a superior survival compared to patients with codon 12 mutations (11). Epidemiologic studies suggest that codon 13 mutant tumors may be more prevalent in African Americans (12) and in patients with hereditary non polyposis coli (HNPCC) syndrome (13).

What are the clinical implications of these data for patient care of patients with a KRAS codon G13D mutation? Due to the relatively infrequent prevalence of tumors with this specific mutation the numbers of patients evaluated in this pooled analysis with a KRAS codon 13 mutation was relatively small, leading to results sufficiently inconclusive to be practice changing. Future studies, likely involving larger pooled analysis of prospective biomarker studies, will be necessary to better understand the differences in biology between these tumors, as well as the full biomarker implications of different KRAS mutations. Such clinical studies will take a long time to accrue with the data being slow to mature. Is there any way to expedite anti-EGFR biomarker assessment? Tumor registries with clinical data linked to tumor molecular studies may produce sufficient numbers of patients to answer this questions which will not likely be answered by a prospective clinical trials. Such biomarker tumor registries may provide additional information regarding the less frequently observed KRAS codon 61 or 146 mutations.

Given the complexities and heterogeneity of KRAS mutations in CRC it may be worthwhile evaluating other potential biomarkers of anti-EGFR efficacy, particularly one that might predict efficacy. To date only tumor amphiregulin and epiregulin gene expression (14), and tumor EGFR copy number have been demonstrated to be predictive of anti-EGFR efficacy (15) although the levels determined to be predictive of response have not been uniformly established.

The era of targeted therapeutics has led to increasingly more specific identification of subsets of patients most likely to benefit from these signal transduction pathway inhibitors. Principally large randomized clinical trials will significantly increase our understanding of how best to utilize these biomarkers, and refine how they are utilized; identifying low prevalence molecular subgroups of CRC may require large tumor registries to determine their biomarker implications.

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