The Role of KRAS Mutation Testing in the Management of Colorectal Cancer
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Retrospective analyses from several recent large clinical trials in metastatic colorectal cancer (mCRC) have examined the role of mutations in the KRAS gene with the response to treatment using the epidermal growth factor receptor (EGFR) monoclonal antibody inhibitors cetuximab and panitumumab.1-8 These data show that both of these agents are ineffective in patients with KRAS mutation. Recently published guidelines from the National Comprehensive Cancer Network9 and the American Society of Clinical Oncology10 recommend KRAS mutation testing as part of the evaluation of mCRC patients who are being considered for anti-EGFR therapy.

EGFR is overexpressed in a large majority of colon cancers, yet there has been poor correlation between EGFR expression by immunohistochemistry and treatment response. This lack of correlation suggests that downstream effectors may be as important as EGFR expression for treatment response. Activation of EGFR triggers multiple signaling pathways resulting in promotion of tumor growth, inhibition of apoptosis, vascular proliferation, invasion, and metastasis. The most important of these pathways for CRC appears to be the Ras signaling pathway.11 Ras proteins are small GTPases, and activated Ras interacts with more than 20 different effectors, KRAS has been long known to be involved in the development and progression of CRC12 and is mutated in about 40% of CRC. The KRAS mutations most commonly found in CRC are at codons 12 and 13 and prevent dephosphorylation and inactivation of the protein, causing it to be permanently switched on, independent of EGFR-mediated signaling. Thus, a mutated KRAS protein would not likely be affected by inhibition of EGFR.

Although there is currently no FDA-approved test for the detection of KRAS mutations, several tests are commercially available. A recently presented abstract that examined 40 formalin-fixed paraffin embedded (FFPE) CRC tissues showed that, despite different methodologies, these four tests yielded comparable results,13 although allele-specific hybridization methods (HistoGeneX and Genzyme) had the highest correlation with the reference methodology of direct sequencing. The KRAS mutation test may be performed on fresh, frozen, or FFPE tissue. In contrast to HER2 expression in breast cancer, KRAS mutation occurs early in CRC carcinogenesis and is unlikely to change during disease progression. Thus, although not confirmed by prospective studies, current practice is not to re-biopsy a tumor recurrence for KRAS testing if there is sufficient material available from the previous biopsy or resection.

Pathologists play an essential role in KRAS testing, whether or not testing is performed in their own laboratory. First, specimens must be handled with careful attention to fixation in
anticipation of potential genetic testing. Second, appropriate tumor tissue for testing must be selected. Third, pathologists must be aware of which KRAS mutation detection methodology is utilized in their reference laboratories and evaluate the quality processes that are used to ensure reliable results. Finally, pathologists can consult with oncologists in the appropriate use of this test and interpretation of the results.

Retrospective analyses of clinical trials have consistently demonstrated that patients with mCRC and mutant KRAS are unlikely to benefit from the addition of cetuximab or panitumumab to a chemotherapy regimen. Testing for KRAS mutation in this setting is now recommended and marks a paradigm shift in the management of these patients.

References


