Commentary on ”KRAS Mutation Status Is Predictive of Response to Cetuximab Therapy in Colorectal Cancer”

Laura E. Benjamin

Ten years ago, Cancer Research published a translational science report by researchers in France describing the relationship between genetics and outcome for patients with metastatic colorectal cancer treated with the newest targeted therapy cetuximab. Lièvre and colleagues studied 30 patients and made a seminal observation correlating ras mutation to cetuximab failure that has guided therapy in colorectal cancer ever since, and that could arguably be credited with kicking off a new era in precision medicine by identifying a critical biomarker that was not simply an activating mutation in the drug's target (1). The role of ras mutation in colorectal cancer had been appreciated for some time. In two seminal research manuscripts published in the New England Journal of Medicine (1987) and Nature (1988), Johannes Bos, Eric Fearon, and Bert Vogelstein and colleagues from the Netherlands described the prevalence of ras mutations as well as the basic concepts of oncogene and tumor suppression alterations directing the tumorigenesis process in the colon (2, 3).

The small New York–based biotech company, ImClone Systems, developed a chimeric blocking mAb to EGFR for cancer therapy. Leading indications included head and neck cancer and colon cancer, based on early clinical activity and literature regarding EGFR prevalence in these indications. Ten years later, the 75th Anniversary Commentary issued by this journal concludes that EGFR is a critical biomarker to be integrated into the future diagnostic process for colorectal cancer and other malignancies (4). Although retrospective, this conclusion is likely to have been influenced by the positive EGFR status of the patients studied by Lièvre and colleagues (1) and others (5, 6). In addition, it has continued for nearly a decade for the FDA to retrospectively change the label of cetuximab (Erbitux) and panitumumab (Vectibix) to require KRAS exon 2 wild-type status as a prerequisite for treatment of colorectal cancer in 2009. Since this time the analysis of mutations and clinical benefit has continued and expanded in recent years to assess mutations in all isoforms and exons of Ras and other key signaling pathways. A compilation of metadata from 22 studies that include 2,395 patients identified additional mutations in KRAS exons 3 and 4, NRAS, BRA, PI3KCA, and Pten as having a negative predictive value for therapeutic anti-EGFR antibodies in colorectal cancer (10). At this time, both the United States and European Societies for Clinical Oncology (ASCO and ESMO) recommend expanded Ras testing for colorectal patients to help guide the choice of therapy (http://gicasym.org/asco-updates-guideline-include-testing-new-ras-mutations and http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000558/WC500155463.pdf).

The initial report by Lièvre and colleagues (1) is an excellent example of how small translational, yet exploratory, studies have been and are critical to advances in patient care. In recent years, the FDA and other regulatory bodies have put in place more systematic regulatory path for the inclusion of patient stratification based on diagnostics in drug labels. As these guidelines are relatively new and being tested, it is likely that the ultimate decisions for genetic testing or other diagnostic measures will further evolve in the coming years, adding to the already complex process of new drug approvals. However, as was the case in 2009, a more systematic astounding volume of data was sufficient for the FDA to retrospectively change the label of cetuximab (Erbitux) and panitumumab (Vectibix) to require KRAS exon 2 wild-type status as a prerequisite for treatment of colorectal cancer in 2009. Since this time the analysis of mutations and clinical benefit has continued and expanded in recent years to assess mutations in all isoforms and exons of Ras and other key signaling pathways. A compilation of metadata from 22 studies that include 2,395 patients identified additional mutations in KRAS exons 3 and 4, NRAS, BRA, PI3KCA, and PTEN as having a negative predictive value for therapeutic anti-EGFR antibodies in colorectal cancer (10). At this time, both the United States and European Societies for Clinical Oncology (ASCO and ESMO) recommend expanded Ras testing for colorectal patients to help guide the choice of therapy (http://gicasym.org/asco-updates-guideline-include-testing-new-ras-mutations and http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000558/WC500155463.pdf).

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when Kras exon 2 testing became mandatory for anti-EGFR antibody use in colorectal cancer, the regulatory agencies will need to remain open-minded and nimble to take advantage of new knowledge and new technology associated with future diagnostics, as it is evermore imperative that patient selection become a standard component of oncology drug use in this age of personalized care.

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References

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