EDITORIALS

Targeting EGFR in Colorectal Cancer

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In the United States, cancer is the most common cause of death among people under the age of 85 years, and colorectal cancer is the second most common cause of death from cancer.[1] Chemotherapy for colorectal cancer has until recently typically consisted of the empirical use of cytotoxic agents guided by the results of controlled clinical trials. Cancer therapy has now entered a new era, however, owing to remarkable advances in our understanding of the nature of molecular and biochemical events involved in the process of carcinogenesis and tumor growth. Biologically targeted therapies are now commonly used as part of the standard therapy for many types of cancer, including colorectal cancer.[2]

If, as we believe, the process of carcinogenesis is largely driven by mutations or mutation-like events, and the biochemical consequences of those events can be understood, then this knowledge should lead to effective targeted therapeutic strategies. An outstanding example of this approach is the article by Karapetis et al. in this issue of the *Journal*.[3] Karapetis et al. found that among patients with advanced, refractory colorectal cancer, the therapeutic benefit of cetuximab, an antibody to the epidermal growth factor receptor (EGFR), is limited to those who have a cancer that bears unmutated copies of the *K-ras* gene. The foundations of this work are numerous laboratory investigations that have defined the multiple components of the EGFR signaling pathways[4] and data showing that one or more of these pathways are commonly activated in colorectal cancer. These findings led to preclinical and then clinical trials of EGFR inhibitors. Antibodies that bind to the EGFR and prevent it from performing its function, namely, cell signaling, have been shown to modestly improve progression-free survival,[5] overall survival,[6] and the quality of life among patients with previously treated colorectal cancer.

Karapetis et al. used an understanding of the mechanisms of EGFR signaling to define subgroups of patients who might be expected to have a differential response to anti-EGFR antibody therapy. *K-ras* is a guanosine triphosphate (GTP)–binding protein that acts as a critical on–off switch in cellular growth and survival pathways.[7] It is a central component of the mitogen-activated protein kinase (MAPK) pathway, which is one of the pathways activated by EGFR signaling. Mutations of *K-ras* that result in constitutive activation of the MAPK pathway downstream of the EGFR occur in about 40% of colorectal cancers.[8] Karapetis et al. used stored tumor samples from patients enrolled in the CO.17 trial, which was conducted by the National Cancer Institute of Canada Clinical Trials Group in collaboration with the Australasian Gastro-Intestinal Trials Group. That trial showed that cetuximab plus best supportive care resulted in a small improvement in survival and quality of life as compared with best supportive care alone among patients with advanced, previously treated colorectal cancer.[6] The retrospective correlative analysis performed by Karapetis et al. showed that the benefit of cetuximab treatment was confined to patients who had a tumor with no *K-ras* mutations — it had little or no effect in the presence of a *K-ras* mutation — and that the benefit was not due to a prognostic effect of *K-ras* mutations. This finding is consistent with findings in previous studies showing that the benefits of the anti-EGFR antibodies cetuximab[9,10] and panitumumab[11] among patients with colorectal cancer are limited to those

who have colorectal cancers with wild-type *K-ras* genes. The CO.17 trial is unique, however, in that it compared cetuximab plus best supportive care to best supportive care alone without crossover or other chemotherapy agents and it showed, for the first time, an overall survival benefit of cetuximab.

Previous biomarkers that were developed to predict the efficacy of anti-EGFR antibodies in patients with colorectal cancer exemplify the pitfalls of making assumptions about drug-target biology. Food and Drug Administration (FDA) approval of both cetuximab and panitumumab for the treatment of colorectal cancer included a requirement that there be positive immunohistochemical staining for the presence of EGFR in the tumor. On the basis of experience with trastuzumab for breast cancer, it seemed reasonable that expression of the target would be required for efficacy, but this does not appear to be the case in colorectal cancer. The degree of expression of EGFR in colorectal cancers, as estimated by immunohistochemical analysis, does not appear to predict the efficacy of these antibodies.[12,13] Since there was considerable concern as to whether the treatment of patients who had colorectal tumors that did not express EGFR would be reimbursed by insurers, one must wonder how many thousands of patients were unable to receive these drugs because of an FDA approval that required expression of a misleading biomarker.

K-ras mutational analysis has advantages over attempts to predict responsiveness to anti-EGFR antibodies with the use of immunohistochemical analysis. DNA is stable in fixed tissue samples, and mutational analysis is therefore less likely than immunohistochemical analysis to be affected by fixation and storage. Moreover, mutational analysis is a yes-or-no result: either the mutation is present or it is not, whereas immunohistochemical analysis entails subjective grading of the intensity of the staining. Since *K-ras* mutations appear early in the development of colorectal cancer,[14] there is concordance in mutational status between the primary cancer and metastases. And since the vast majority of *K-ras* mutations occur in only three codons,[7] polymerase-chain-reaction assays can detect them; sequencing of large numbers of exons is unnecessary.

The results of the study by Karapetis et al. have biologic and clinical implications. The lack of effectiveness of EGFR inhibition in patients who have cancers with *K-ras* mutations highlights the biologic relevance of the MAPK pathway of EGFR signaling to the carcinogenic process. If a signaling pathway other than MAPK were mediating the procarcinogenic effect of persistent EGFR activation, then MAPK activation driven by a mutated *K-ras* gene would not be expected to prevent the benefit of EGFR-targeted antibodies. The results also suggest that other mutations that activate the MAPK pathway in colorectal cancer might also hinder the effectiveness of anti-EGFR therapy. The relevance of this point is that about 15% of colorectal cancers have activating mutations in B-type Raf kinase (*BRAF*), the gene for a kinase immediately downstream of *K-ras* in the MAPK pathway. It is possible that colorectal tumors with *BRAF* mutations would also be unresponsive to anti-EGFR therapy and that kinase inhibitors that block MAPK signaling downstream of *K-ras* and *BRAF* could have efficacy among patients who have cancers with these mutations. These possibilities are being tested.

The data from Karapetis et al. and from previous studies[9-11] lead to the reasonable recommendation that all patients with advanced colorectal cancer who are being considered for anti-EGFR therapy should undergo *K-ras* testing, and if the cancer bears a mutated *K-ras* gene, they should not receive an antibody that targets EGFR. Data from more than 2000 patients involving two different drugs show that the benefits of anti-EGFR antibodies are limited to the subgroup with wild-type *K-ras* tumors. These results have already had important consequences. The European Medicines Agency has approved panitumumab for the treatment of patients with wild-type *K-ras* tumors only. To our knowledge, this is the first example of the approval of a drug therapy for solid tumors that is based on a genetic test. Furthermore, the 10 cetuximab studies sponsored by the National Cancer Institute are being amended to include *K-ras* testing. There is no FDA-approved test for *K-ras* mutational status, but that is likely to change soon. Finally, these data on *K-ras* highlight the value of banking specimens obtained in large clinical trials to allow subsequent identification of patients who benefited, even when the putative markers are unknown. These efforts are frequently difficult to fund, but, as the study by Karapetis et al. shows, they can be cost-saving; limiting

expensive anti-EGFR antibody therapy to the subgroup of patients with wild-type *K-ras* colorectal cancers will save millions of dollars that would otherwise have been spent on patients who had no chance of benefit.

Finally, lest the field of EGFR biology become carried away with the success of *K-ras* as a molecular marker, it should be noted that the difference in survival between the groups of patients identified by *K-ras* testing is small. The response rate with cetuximab treatment among patients with wild-type *K-ras* tumors remains less than 15%, with only a modest overall survival benefit over those given best supportive care alone (median survival, 9.5 months with cetuximab vs. 4.8 months with best supportive care alone). There was no effect of cetuximab on median survival among patients with mutated *K-ras* tumors (4.5 months with cetuximab vs. 4.6 months with best supportive care alone). Although the 5-month improvement in median survival among the patients with wild type *K-ras* tumors who were treated with cetuximab generates excitement among oncologists, who are accustomed to such marginal improvements, the reaction among patients with colorectal cancer and other persons in the general population may be more muted. In fact, in countries that include an analysis of cost-effectiveness as part of the approval process, EGFR-targeting antibodies are frequently not approved, owing to a marginal benefit at high cost. Perhaps further molecular analysis will yield other markers that will identify patients who benefit from EGFR-targeting antibodies and will point to other targets and combination strategies needed to overcome drug resistance.

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TLR Polymorphisms and the Risk of Invasive Fungal Infections

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Allogeneic hematopoietic stem-cell transplantation is a potentially lifesaving cancer therapy that, at least temporarily, renders patients highly immunocompromised and vulnerable to infection. *Aspergillus fumigatus*, a common environmental fungus that causes invasive infections in immunocompromised persons, is particularly problematic in patients who have undergone this treatment.[1] Although the risk of the development of aspergillosis correlates with the degree of immunosuppression and the intensity of exposure to fungal spores, these factors alone do not explain why this infection develops in approximately 5 to 10% of patients who have received these transplants,