

KRAS Testing: Optimizing Cancer Therapy

Bob Carlson, MHA, Senior Contributing Editor

When you're getting chemotherapy, it's reassuring to know that the drugs you're given have a chance of working. That reassurance is what the KRAS test provides to metastatic colorectal cancer (mCRC) patients being treated with the epidermal growth factor receptor (EGFR) blockers cetuximab (Erbix) or panitumumab (Vectibix).

The buzz about KRAS (pronounced KAY-rass) testing started at the 2008 American Society of Clinical Oncology annual meeting. Five randomized controlled trials concluded that mCRC patients whose tumor tissue had KRAS gene mutations (between a third and half of patients tested) do not benefit from cetuximab or panitumumab, whereas some patients with "wild-type" KRAS do.

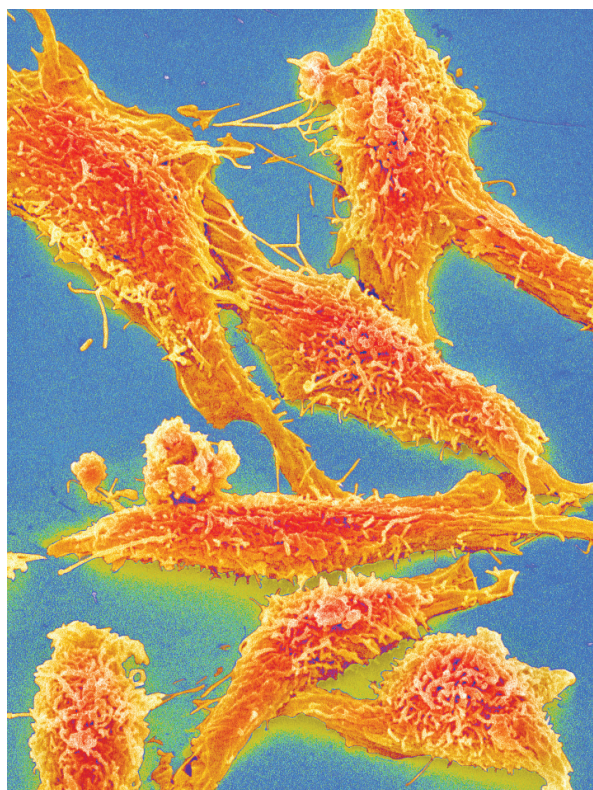
"The data were so robust that before we had time to develop a guideline, we wanted to, along with the NCCN [National Comprehensive Cancer Network], get the word out to practicing oncologists that we need to utilize this test to help our patients receive appropriate therapy and spare those who have no chance of benefit," recalls Jennifer C. Obel, MD, a gastrointestinal oncologist and attending physician at NorthShore University HealthSystem in Evanston, Ill., and assistant clinical professor at the University of Chicago School of Medicine.

To get KRAS testing into practice as fast as possible, NCCN updated its guidelines for colon and rectal cancers five months later (NCCN 2009), and in April 2009, ASCO published its first-ever Provisional Clinical Opinion (PCO) in the *Journal of Clinical Oncology* (Allegra 2009).

The PCO states, "Based on systematic reviews of the relevant literature, all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for KRAS mutations in a Clinical Laboratory Improvement Amendments-accredited laboratory. If KRAS mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy."

ASCO credits the BlueCross BlueShield Association Technology Evaluation Center (TEC) in Chicago with doing most of the literature review. The TEC had been evaluating tumor cell KRAS mutation status as a predictor of nonresponse to EGFR-targeted therapy in patients with mCRC, and published its assessment in January 2009. ASCO decided to base its PCO on that assessment.

According to Eli Lilly & Co. (parent of ImClone, man-



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Colored scanning electron micrograph of colon cancer cells.

ufacturer of cetuximab), the cost of cetuximab is roughly \$10,000 for a 4-week cycle of treatment. Based on the phase 3 trial dosing, the average wholesale list price for a course of treatment would be approximately \$18,000 (7 doses) to \$38,000 (16 doses). Extrapolating from that, a single dose of cetuximab administered once a week would cost approximately \$2,400 just for the drug. For Amgen's panitumumab, administered once every two weeks, that cost is \$4,245. An anti-EGFR regimen for patients with advanced CRC can range between 7 and 16 weeks. Add it all up, and limiting anti-EGFR therapy to patients with wild-type KRAS tumors could save a tidy \$604 million in annual drug costs alone. That was the estimate in an economic analysis presented at ASCO's 2009 Gastrointestinal Cancers Symposium (Shankaran 2009).

That's good news when it comes to reining in health-care costs. And avoiding futile therapy can also eliminate the side effects of cetuximab or panitumumab.

PERSONALIZED MEDICINE

“Our patients with advanced colon cancer could be in the infusion clinic once a week for 12 or 16 weeks, getting a drug that will not prolong their life,” Obel says.

Unnecessary exposure to adverse events is another concern. The cetuximab label cites skin rash/desquamation, fatigue, abdominal pain, dyspnea, constipation, and insomnia as adverse events in 10 percent or more of patients with advanced colorectal carcinoma. If irinotecan is added to the regimen, frequent AEs also include asthenia/malaise (73 percent) and nausea (55 percent). Patients taking panitumumab may experience those AEs plus ocular toxicities and exacerbation of dermatologic toxicity with exposure to sunlight. The labels for cetuximab and for panitumumab, both updated last July, now recommend that all mCRC patients be tested for KRAS mutational status.

A GOOD THING

Charles (not his real name), who runs a large company, can tell you all about the acneiform rash that covered his face, chest, and back when he was on cetuximab from October 2008 until March 2009. He’s been Obel’s patient since his 2004 diagnosis with colorectal cancer. After a hemicolectomy, Charles had surgeries to remove

“It’s not ‘one size fits all’ for colon cancer therapy. Determining the different gene mutations in different tumors will help us to really personalize care.”

two small metastatic tumors from his liver. He credits a regimen of FOLFOX 5 (a combination of oxaliplatin, leucovorin, and 5-fluorouracil) plus the angiogenesis inhibitor bevacizumab (Avastin) with two years of progression-free survival.

“Anything that suggests that what I have won’t block the efficacy of the drugs is a good thing,” says Charles, referring to KRAS testing. “But I’d feel a lot happier knowing that an angiogenesis inhibitor like Avastin could keep this thing in check forever than [knowing] that Erbitux extends survival ... by weeks on average.”

Actually, treatment with cetuximab improved median overall survival to 9.5 months in patients with wild-type KRAS tumors, compared with 4.8 months in patients who received best supportive care alone, according to a study (Karapetis 2008) of 572 patients with mCRC refractory to other therapies. Among patients with KRAS-mutated tumors, there was no difference, regardless of whether they were treated with an EGFR inhibitor. Overall survival for patients receiving cetuximab was 6.1 months compared with 4.6 months for patients receiving best supportive care.

But Charles’ dissatisfaction with the relative ineffectiveness of current therapies for mCRC is understandable. When overall survival is measured in months, you know there’s work to be done.

“Unfortunately, we are not curing patients with metastatic colon cancer with these drugs,” Obel acknowledges. “Our current treatments help patients live longer with fewer symptoms, but our overarching goal is for patients to be cured, even in the advanced stage.”

Many studies are now underway to improve the prognosis for the 30,000 patients diagnosed with mCRC annually in the United States. Raymond Hayes, a 43-year-old IT project manager with stage 3 mCRC, is in one of those trials.* His oncologist at the Lehigh Valley Physician Group, in Allentown, Pa., recommended him for the trial after part of Hayes’s colon was removed in September.

Cetuximab and panitumumab are typically prescribed as second- or third-line therapies after disease progression on FOLFOX 5 and FOLFIRI (folinic acid, fluorouracil, and oxaliplatin) with or without bevacizumab and/or capecitabine. The trial in which Hayes is enrolled compares the effectiveness of three different chemotherapy regimens with or without cetuximab as first-line therapy, in patients after colon cancer surgery. Hayes spoke with me via telephone while he was being infused with his weekly regimen of drugs at Lehigh Valley Hospital.

“Since my whole desire to be part of this clinical trial

was to increase my chances of avoiding a recurrence of cancer in the future, you can imagine how important I considered the results of this KRAS test,” Hayes says. “It was the determining factor for whether I could participate and hopefully increase my chances of beating this cancer.”

NOT ONE SIZE FITS ALL

Hayes’ wild-type KRAS status made him eligible for this trial, but only 40 percent to 60 percent of patients with wild-type KRAS tumors respond to anti-EGFR treatment. That suggests there may be additional biomarkers that are predictive of anti-EGFR effectiveness, and the quest to identify those biomarkers keeps researchers busy. For example, one study (Laurent-Puig 2009) found that BRAF gene mutations and PTEN gene expression were associated with shorter overall survival in patients with KRAS wild-type tumors who were on cetuximab therapy.

The confounding thing is that colorectal cancer is actually many different cancers. In 2007, Laura Wood and colleagues sequenced genes in CRC tumors from 11

* Comparison of Combination Chemotherapy Regimens With or Without Cetuximab in Treating Patients Who Have Undergone Surgery for Stage III Colon Cancer. ClinicalTrials.gov Identifier NCT00079274. <<http://www.clinicaltrials.gov/ct2/show/NCT00079274?term=n0147&rank=1>>. Accessed Dec. 16, 2009.

patients. As the team reported in *Science*, each patient had an average of 15 mutations likely to contribute to tumor behavior, “but very few of these defects were common among the different tumors.” Commenting on this finding, Monica Bertagnolli noted in an editorial last month in the *Journal of Clinical Oncology* that this genomic heterogeneity does not take into account other determinants of tumor biology, “such as gene and protein expression, immune response, and epithelial-stromal interactions.”

“We’re going to find that there are actually different types of colon cancer based on these molecular profiles, that it’s not ‘one size fits all’ for colon cancer therapy, and that there are going to be subset populations even within this one disease,” Obel predicts. “That is, I think, where we’ll be in 10 years — determining the different gene mutations in different tumors that will help us to really personalize care.”

Patients like Charles and Hayes want to be around when that happens. “My goal is to try to keep this thing at bay until the next breakthrough comes,” says Charles.

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Bob Carlson, MHA, writes exclusively about healthcare. He lives near Zionsville, Ind.

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