Adding drug to chemotherapy following colon cancer surgery does not improve disease-free survival

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Adding the drug cetuximab to a regimen of drugs used for the treatment of patients following surgery for stage III colon cancer did not result in improved disease-free survival, according to a study in the April 4 issue of *JAMA*.

Patients who have surgery for removal of stage III colon cancer have a 50 percent chance of cure. Multiple trials have established the benefit of chemotherapy after surgery in reducing the recurrence risk. "Specifically, [the drugs] leucovorin, fluorouracil, and oxaliplatin (FOLFOX or slightly different method, FLOX) provides significant benefit in both disease-free and overall survival compared with the prior standard of fluorouracil and leucovorin," according to background information in the article.

In the setting of metastatic colorectal cancer, the drugs cetuximab and panitumumab, alone and in combination with chemotherapy, have provided additional benefit to that obtained with chemotherapy alone. "This benefit, however, is limited to patients with tumors expressing the wild-type [a strain used as a standard reference to compare any mutant derivatives] form of the gene KRAS as opposed to those with the mutated form of KRAS," the authors write.

Steven R. Alberts, M.D., of the Mayo Clinic, Rochester, M inn., and colleagues conducted a study to assess the potential benefit of cetuximab

added to the modified sixth version of the FOLFOX regimen (mFOLFOX6) in patients with resected stage III wild-type KRAS colon cancer. Patient enrollment began February 2004 and was permanently halted on November 25, 2009, after the second planned interim analysis demonstrated a low probability that disease-free survival of the cetuximab group would surpass that of the mFOLFOX6-only group. A total of 2,686 patients comprised this analysis cohort (1,863 patients with wild-type KRAS, 717 patients with mutated KRAS, and 106 patients with indeterminate KRAS). The primary randomized comparison was 12 biweekly cycles of mFOLFOX6 with and without cetuximab. Median follow-up was 28 months.

The researchers found that the trial demonstrated no benefit when adding cetuximab. Three-year disease-free survival for mFOLFOX6 alone was 74.6 percent vs. 71.5 percent with the addition of cetuximab in patients with wild-type KRAS, and 67.1 percent vs. 65.0 percent in patients with mutated KRAS, with no evidence of benefit in any individual subgroup. Also, both time-to-recurrence and overall survival were not significantly different between treatment groups.

"Among all patients, grade 3 or higher adverse events (72.5 percent vs. 52.3 percent) and failure to complete 12 cycles (33 percent vs. 23 percent) were significantly higher with cetuximab," the authors write. "Increased toxicity and greater detrimental differences in all outcomes were observed in patients aged 70 years or older."

The researchers add that the reasons for the lack of benefit of mFOLFOX6 with cetuximab in the adjuvant setting remain unclear.

"In this randomized phase 3 trial for patients with resected stage III colon cancer expressing wild-type KRAS mutations, the addition of cetuximab to mFOLFOX6 did not improve disease-free or overall survival in contradistinction to the original study of cetuximab combined

with FOLFOX in metastatic colorectal cancer," the authors write. "New approaches are needed to identify drugs that may be of benefit in adjuvant therapy, because as shown in our trial promising activity in the metastatic setting did not translate into adjuvant therapy benefit and underscores the importance of performing clinical trials."

In an accompanying editorial, Neil H. Segal, M.D., Ph.D., and Leonard B. Saltz, M.D., of Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, write that although the negative results of this trial are surprising, this pattern has been observed before.

"The inescapable conclusion is that efficacy in the metastatic setting does not reliably predict efficacy in the adjuvant setting. The role of adjuvant chemotherapy does not involve treating the tumor that the surgeon has removed, but rather attempts to eradicate whatever occult micrometastatic disease may still be present after surgery. If there are no micrometastases, surgery is curative and adjuvant chemotherapy is unnecessary. If micrometastases are present, the long-term health of the patient will depend on whether the chemotherapy can destroy all remaining micrometastases."

More information: *JAMA*. 2012;307[13]:1383-1393.
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