Drug that helps metastatic colon cancer of no benefit in less advanced tumors

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To the surprise of researchers at Mayo Clinic who led a national clinical trial, a targeted therapy that provides benefit to patients with metastatic colon cancer has failed to help patients with less advanced, stage III cancer. In fact, patients who used the agent, cetuximab, with chemotherapy had outcomes slightly inferior to patients treated with chemotherapy alone.

The phase III North Central Cancer Treatment Group (NCCTG) study, sponsored by the National Cancer Institute (NCI), was closed to patient accrual in November 2009 after a planned interim analysis demonstrating a lack of benefit from the addition of cetuximab to standard chemotherapy. The first public discussion of the study and results presented in a press conference June 6 at the annual meeting of the American Society of Clinical Oncology (ASCO).

In theory, many of the patients enrolled on this trial should have benefited from the addition of cetuximab to chemotherapy, says Steven Alberts, M.D., the Mayo Clinic oncologist who led the clinical trial. All of the patients enrolled in the trial had colon cancers that had spread to the nearby lymph nodes (stage III), but not beyond. To be eligible for the trial, patients first had to have the cancer completely removed with surgery. These patients also had a normal (wild-type) KRAS gene in their tumor, which previously has been shown necessary to have the potential for cetuximab to work.

"The sum of data to date from trials for metastatic colorectal cancer

suggested that cetuximab would provide benefit in these stage III patients with KRAS wild-type tumors, and so our findings are unexpected," Dr. Alberts says. "It is difficult to understand how an agent that helps patients with metastatic cancer is not beneficial to those with less advanced disease. At this point we are focusing our efforts on identifying a biological explanation for these findings."

With more than 3,000 patients enrolled, the study was one of the largest clinical trials yet performed testing cetuximab with the commonly-used FOLFOX chemotherapy following surgery in patients with colon cancer. It was expected that adding cetuximab to FOLFOX would provide benefit in stage III colon cancer patients, and would lead to Food and Drug Administration (FDA)-approval for that indication, Dr. Alberts says. Currently, the FDA has only approved cetuximab for metastatic colon cancer and the drug should continue to be used in that setting as clinically appropriate, he says.

"Based on what we found, any use of cetuximab in stage III colon cancer is not supported by the results of our trial," he says.

According to Dr. Alberts, this is the only U.S. study to have looked at the use of chemotherapy and cetuximab in phase III colon cancer patients, but a European clinical trial is ongoing and first results are expected next year.

The randomized clinical trial had multiple arms, but the most important were the two that tested FOLFOX with or without cetuximab. This particular analysis looked only at the 1,864 enrolled patients with a normal KRAS gene (909 treated with chemotherapy alone and 955 patients treated with both drugs).

Based on a statistical analysis of the outcomes at the three-year mark post-treatment, the researchers found that those treated with

chemotherapy alone (without cetuximab) had a 76 percent disease-free survival (alive and with no disease recurrence), compared to 72 percent in patients who used both therapies. Overall survival in all patients to date is also better in patients who did not receive cetuximab. However, as this study was stopped early after a median follow-up of approximately two years, "Follow-up in regard to survival is short at this point," Dr. Alberts says.

The researchers also concluded that while there were no differences in toxicity between treatment groups in patients younger than 70, there was increased toxicity as well as greater differences in outcomes in patients aged 70 and older.

The researchers have theories as to why stage III colon cancer patients did not benefit from cetuximab, but no evidence yet. Two favored ideas are that cetuximab could be switching on, or increasing activity, in molecular pathways that promote cellular growth, or could be creating resistance to the effects of chemotherapy.

"The most critical question from this trial is why a difference exists between patients with stage III disease, where cetuximab is not of benefit, and patients with metastatic cancer, where cetuximab does provide benefit," Dr. Alberts says. "We aim to find out."

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