Gastric Cancer: Trastuzumab Trial Results
Spur Search for Other Targets

By Karyn Hede

Improving outcomes for advanced gastric cancer patients has been frustratingly difficult to achieve. Despite many trials, no chemotherapy regimen has provided a median survival beyond 1 year.

That’s why many were stunned when results from the first randomized prospective phase III trial testing trastuzumab (Herceptin) in gastric cancer showed overall survival of 13.8 months in the treatment group, compared with 11.1 months in the control group. Although modest, the 2.7-month improvement was clinically meaningful enough to halt the trial early and has already affected other planned studies.

The results, presented by principal investigator Eric van Cutsem, M.D., of the University Hospital Gasthuisberg, Leuven, Belgium, at the annual American Society of Clinical Oncology meeting, represent the first evidence that HER2 is an important driver of cancer growth in some patients and that targeting HER2 provides a demonstrable benefit. “This is the first targeted agent in gastric cancer that shows a survival benefit,” van Cutsem said during the ASCO presentation. He added that all advanced gastric cancer patients should now be tested for HER2-positive disease.

Although the incidence of gastric cancer in the United States has been on the decline for more than 50 years, worldwide it continues to be the second leading cause of cancer-related deaths, with 800,000 deaths each year, according to the World Health Organization. Because the incidence of stomach cancer in the United States is low and its symptoms are often vague in the early stages, it is usually detected at the harder-to-treat advanced stage when more severe symptoms finally do appear. Standard treatment in the United States is combination high-dose chemotherapy, typically including cisplatin and 5-fluorouracil.

About 20% of gastric tumors overexpress HER2, a similar rate to that seen in breast cancer, where trastuzumab, targeted at HER2, is now a first-line therapy. First approved for metastatic breast cancer in 1998, trastuzumab was quickly tested in HER2-positive, early-stage breast cancer, where it cut the recurrence rate in half compared with chemotherapy alone. Van Cutsem suggested that the next study should look at trastuzumab as adjuvant therapy in patients with earlier gastric cancer after surgery.

At least one researcher involved in the study is already planning such a trial. Atsushi Ohtsu, M.D., Ph.D., director of the research center for innovative oncology at the National Cancer Center Hospital in Chiba, Japan, said that plans are under way for an adjuvant trial in Japan. “This trial will surely change medical practice in Japan, though we have to wait until the approval

“Although it is only a single trial, in my mind it is a very persuasive single trial....”

Richard Schilsky, M.D.
of trastuzumab with medical reimbursement for gastric cancer,” he said.

Some physicians were so impressed by the study result that they planned to start testing their own patients for HER2 expression levels immediately.

“Although it is only a single trial, in my mind it is a very persuasive single trial, certainly persuasive enough that now patients with metastatic gastric cancer should have their tumors tested for whether they are HER2 positive or not,” said Richard Schilsky, M.D., a medical oncologist specializing in gastrointestinal cancers at the University of Chicago and outgoing ASCO president. “If I had a patient with gastric cancer, I would have their tumor tested for HER2 expression now and would most likely add [trastuzumab] to their regimen if they were HER2 positive, particularly if they were strongly HER2 positive.”

Schilsky pointed out that delving into the ToGA trial data reveals that patients who had the greatest benefit were those whose tumors were most strongly HER2 positive. In those patients, which included 256 of the 594 total patients in the study, overall survival was 17.9 months.

**Shift to Biologics**

The ToGA results may change how researchers think about gastric cancer. “I think this will have significant impact on how we develop new drugs and new concepts for gastric cancer, going away from just mixing and matching cytotoxics, taking advantage of a molecular characterization and opening up targeted treatment options in addition to chemotherapy, not instead of chemotherapy,” said Heinz-Josef Lenz, M.D., chair of gastrointestinal oncology at the Norris Comprehensive Cancer Center at the University of Southern California, Los Angeles.

Lenz said that the ToGA results are already altering study design for a prospective Southwest Oncology Group clinical trial about to get under way. In that trial, gastric cancer patients will receive either irinotecan or FOLFOX (a combination therapy of folic acid [leucovorin], 5-fluorouracil, and oxaliplatin). Lenz said that patients enrolled in the trial will now be tested for HER2 and will be treated with trastuzumab if they test positive for HER2 expression. “Knowing molecular characterization in addition to clinical pathological staging will impact the outcome of this patient population,” said Lenz. He pointed out that some subgroups of gastric cancer patients may see an even greater benefit than the overall ToGA trial suggests.

“We all know that the gastric cancers are a very heterogeneous group,” he said. Histologists divide the disease into two subgroups, intestinal and diffuse, on the basis of their appearance. But within those groups, different patterns of genetic alterations occur, Lenz said. Although overall 22% of patients tested for inclusion in the ToGA trial were HER2 positive, the subgroups varied widely in HER2 expression. Tumors at the esophageal–gastric junction (EGJ) were 35% HER2 positive while those classified as gastric tumors were 20% positive; tumors with diffuse pathology at either site were just 6% positive for HER2. Similarly, HER2-positive rates varied widely by country. In Denmark, France, Germany, and the United Kingdom, more patients develop EGJ cancer (50%, 33%, 27%, and 34%, respectively), and these countries reported the highest HER2 rates (26%, 28%, 22%, and 28%, respectively). Asian and South American countries had low percentages of EGJ and low HER2 rates, varying from 3% to 15%.

“We just really need to look at the basic science of gastric cancer right now and start choosing out the targets that may be most relevant,” said Jordan Berlin, M.D., clinical director of gastrointestinal oncology at Vanderbilt–Ingram Cancer Center, Nashville, Tenn.

**Other Targets**

For example, Berlin pointed out that members of the epidermal growth factor receptor (EGFR) family, which includes HER2, can bind to each other to become activated. Moreover, EGFR and EGFR overexpression are associated with gastric tumor aggressiveness and poor outcomes. He suggested that looking at inhibitors that target more than one EGFR family member might make sense.

Two EGFR inhibitors, lapatinib (Tykerb) and cetuximab (Erbitux), are already being tested in early-stage clinical trials for gastric cancer. Cetuximab, a U.S. Food and Drug Administration–approved EGFR inhibitor for colon, head, and neck cancers, is considered investigational for gastric cancer. One study, cosponsored by USC’s Norris Cancer Center, has nearly completed accruing patients to test cetuximab in combination with two chemotherapy agents, capecitabine (Xeloda) and oxaliplatin (Eloxatin), but results of the study have not been published. Other phase II studies have been promising enough that an international phase III study, the EXPAND trial, is under way.

Another potential target in gastric cancer is heat shock protein 90, according to Lenz. In recent years investigators have found that Hsp90, a protein chaperone complex responsible for regulating cell proliferation and survival, regulates EGFR, HER2, and other oncogenic proteins. Early phase I clinical trials with Hsp90 inhibitors demonstrated unacceptable toxic effects, but newer agents are now entering clinical trials. One such drug, MPC-3100, from Myriad Pharmaceuticals, was approved in April for phase I safety testing. The agent demonstrated anticaner activity in xenograft models of HER2-positive tumors, including gastric cancer, according to Myriad.

One reason that Hsp90 inhibitors are so exciting, Lenz said, is that they target multiple pathways that are activated in gastric cancer. These include cMET, PI3K, mTOR (mammalian target of rapamycin), and AKT pathways, each of which is represented in subgroups of gastric tumors, he said.

Another potential targeted therapy, everolimus (Afinitor), an mTOR inhibitor, is being tested in phase I/II studies in Japan with promising results, according to Ohtsu. A randomized trial comparing everolimus with placebo as a second- or third-line treatment has just started in Japan.

Perhaps the biggest effect of the ToGA trial is that the gastric cancer research community is realizing that it is possible to design and conduct molecularly targeted trials in gastric cancer, as well as to find a way to show an effect in an enriched cohort where patients are selected based on a genetic profile, said Berlin. “Usually when there is a positive trial in a disease that really seems to be substantially different, it will turn the tide for [additional] trials,” he said. “[We hope that] what this will do is spur some research.”

© Oxford University Press 2009. DOI: 10.1093/jnci/djp341