

Trastuzumab in HER2-positive advanced esophagogastric adenocarcinoma

The addition of trastuzumab to standard chemotherapy appears to benefit patients with advanced HER2-positive stomach and esophagogastric cancers.

What's new, what's important

Finding new and effective targets for treatment of cancer is an ongoing challenge for translational scientists. But finding old targets in new cancer types is exciting, especially when the treatments are effective.

The human epidermal growth factor receptor 2 (HER2)/*neu* receptor is a member of the epidermal growth factor receptor family and is overexpressed in many cancers, including breast, ovarian, lung, gastric, and oral cancers. Recent studies have shown that about 20% of patients with esophagogastric cancer are HER2-positive, whether determined by immune histochemistry or fluorescence in situ hybridization.

Clinical trials have shown that the addition of trastuzumab (Herceptin), which targets the HER2 receptor, to standard chemotherapy results in about a 26% reduction in the risk of dying from metastatic esophagogastric cancer. The side effects of trastuzumab are minimal, although patients need to be monitored for cardiac toxicity while taking this drug.

It is exciting to see the role of trastuzumab and HER2 targets expanding to other cancer diagnoses. Hopefully, this research endeavor will open ways for exploring other novel HER2-targeted treatments for gastric cancer and other cancers.

— Jame Abraham, MD
Section Editor

Trastuzumab (Herceptin), a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2) on cancer cells, exhibits activity in human esophagogastric tumors that overexpress HER2. Overexpression of HER2 has been demonstrated in approximately 10%–25% of gastric cancers. Phase II studies have shown activity of trastuzumab when added to standard chemotherapy in the treatment of advanced gastric cancer,^{1,2} a finding that has been confirmed in the recently reported phase III ToGA trial of trastuzumab in combination with chemotherapy for first-line treatment of locally advanced and metastatic diseases.³

Phase II trials

At the 31st Congress of the European Society for Medical Oncology, Nicholas et al reported the initial results of a phase II trial of cisplatin (75 mg/m²), docetaxel (Taxotere; 75 mg/m²), and trastuzumab (6 mg/kg, following a loading dose of 8 mg/kg) given on day 1 of a 21-day cycle in patients with HER2-positive advanced gastric cancer.¹ Of the first five patients enrolled, three had a partial response, one had a complete response, and one had stable disease after 5–11 cycles of treatment. One patient died from upper gastrointestinal bleeding, possibly related to the study treatment or to a migrating stent. Other grade 3/4 toxicities included peripheral neuropathy, abdominal cramping,

and neutropenia in one patient each.

In screening to identify study candidates, HER2 overexpression, defined as fluorescence in situ hybridization (FISH) positivity or a 3+ finding on immunohistochemistry (IHC), was identified in 9 of 55 (16%) advanced cancers of the stomach or gastroesophageal junction.

In another phase II trial, reported by Cortés-Funes and colleagues,² 17 evaluable patients with HER2-overexpressing (IHC 2+ and FISH+ or IHC 3+) advanced stomach or esophagogastric cancer received cisplatin (75 mg/m²) and trastuzumab (loading

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dose of 8 mg/kg, followed by 6 mg/kg thereafter) on day 1 every 21 days. All patients were chemotherapy-naïve at the start of the trial but may have received adjuvant chemotherapy or radiotherapy. After a median of two cycles (range, 1–14), six patients (35%) had a response (one complete, five partial) and three (17%) had stable disease, yielding an overall disease control rate of 52%; four patients had progressive disease, and it was too early to determine outcome in the remaining four patients at the time of reporting.

No grade 4 toxicity was observed; the main grade 3 toxicities were asthenia and nausea/vomiting in three patients each, diarrhea and hypoxemia in two each, and neutropenia in one. In prior experience, these investigators identified a 13.5% rate of HER2 overexpression in advanced stomach or esophagogastric cancer.

Phase III study

Results of the multicenter phase III ToGA trial, reported at the 2009 annual meeting of the American Society of Clinical Oncology by Van

Cutsem and colleagues,³ indicate that the addition of trastuzumab to standard chemotherapy is associated with a survival benefit in first-line treatment of HER2-positive advanced esophagogastric cancer. Central testing of tumors from 3,807 patients showed that 22.1% were HER2-positive (IHC 3+ and/or FISH+). A total of 594 patients with HER2-positive tumors were randomized to receive treatment with trastuzumab plus chemotherapy, consisting of 5-fluorouracil or capecitabine (Xeloda) plus cisplatin, or chemotherapy alone every 21 days for 6 cycles; trastuzumab was continued until disease progression. Median follow-up was 17.1 months.

Median overall survival, the primary endpoint, was significantly prolonged in the trastuzumab plus chemotherapy arm when compared with chemotherapy alone (13.5 months vs 11.1 months; $P = 0.0048$), representing a 26% reduction in the risk of death in the trastuzumab group (hazard ratio, 0.74; 95% confidence interval = 0.60–0.91). The overall response rate was also significantly greater

in the trastuzumab arm (47.3% vs 34.5%; $P = 0.0017$). Safety profiles were similar in the two study groups, with no unexpected adverse events being reported with the addition of trastuzumab to chemotherapy. The two study groups had similar rates of symptomatic congestive heart failure; however, asymptomatic decreases in left ventricular ejection fraction occurred in 4.6% of patients receiving trastuzumab plus chemotherapy versus 1.1% of those receiving chemotherapy alone.

References

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From the Oncologist's Perspective

Welcome to the team: trastuzumab in HER2-positive esophagogastric cancers

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One of the most clinically important presentations in gastrointestinal oncology flew under many radar screens at the June 2009 American Society of Clinical Oncology annual meeting. Dr. Eric Van Cutsem presented the results of the randomized controlled ToGA trial testing the addition of the monoclonal antibody tras-

tuzumab (Herceptin) to standard chemotherapy in advanced esophageal and gastric adenocarcinomas.¹ Dozens of prior clinical trials have attempted to break the 1-year median survival mark in this advanced disease but have consistently come up short.² This study represents the first time that a biologic targeted therapy has proven to be of clinical value in the management of esoph-

agogastric cancers and simultaneously establishes a new standard of care for this worldwide killer.

Dr. George, Assistant Professor of Medicine, Division of Hematology/Oncology, Director of the Gastrointestinal Oncology Program, and Associate Director of the Hematology/Oncology Fellowship Program at the University of Florida College of Medicine, Gainesville, FL, has no conflicts of interest to disclose.

ToGA study

The ToGA study was a well designed, conducted, and reported trial. The two treatment arms were well balanced, and patients were appropriately stratified within each arm. Treatment was limited to only those patients whose tumors overexpressed the target of trastuzumab, human epidermal growth factor receptor 2 (HER2). Nearly 4,000 esophagogastric adenocarcinomas were centrally tested for HER2 overexpression via technologies that are routinely available and in widespread practice for breast cancer.³

HER2 overexpression was defined simply as immunohistochemistry (IHC) 3+ or fluorescence in situ hybridization (FISH) positivity. The incidence of HER2 overexpression was 22%, a rate similar to that seen in breast cancer. Unlike breast cancer, however, the IHC 0/1+ esophagogastric tumors were FISH-positive at nearly the same rate as the IHC 2+/3+ tumors, suggesting that FISH testing may be the more relevant procedure to conduct on these tumor specimens. Importantly, HER2-positive tumors were identified in all histologic subtypes (intestinal, diffuse, mixed) and anatomic locations (gastric body, cardia, gastroesophageal junction).

Reasonable first-line treatment consisted of 5-fluorouracil or capecitabine (Xeloda) plus cisplatin with or without trastuzumab. Doses were

appropriate, and dose intensity was maintained between the two groups. Response rate (47.3% vs 34.5%; $P = 0.0017$) and overall survival, the primary endpoint, favored the experimental arm (13.5 months vs 11.1 months; $P = 0.0048$). Although modest, the hazard ratio of 0.74 implied a 26% reduction in death for patients receiving trastuzumab and resulted in early stopping of the trial. These advantages of trastuzumab therapy were achieved without notable increases in toxicity, except for a slightly higher percentage of patients experiencing an asymptomatic reduction in left ventricular ejection fraction (4.6% in the trastuzumab-plus-chemotherapy arm vs 1.1% in the chemotherapy-only arm).

Based on preplanned subset analysis of survival by HER2 status, the greatest clinical benefit was seen in those patients who were most strongly HER2-positive (ie, IHC 3+/FISH+), with a median survival of 17.9 months.

Other avenues being explored

The race is now on to confirm these findings and further exploit the biologic weaknesses of these tumors with targeted therapies. Alternative chemotherapeutic backbones in combination with trastuzumab are being actively investigated, and plans are under way to begin perioperative studies incorporating trastuzumab.

We also anxiously await the results of numerous ongoing trials incorporating other inhibitors of the epidermal growth factor receptor pathway, such as cetuximab (Erbix) and lapatinib (Tykerb), as well as alternative pathway inhibitors with associated predictive biomarkers.

While we're waiting, all advanced esophagogastric adenocarcinomas should now be routinely tested for HER2 overexpression to identify this subgroup of patients who can take advantage of this paradigm-shifting discovery. Much like with *KRAS* testing in colorectal cancer, predictive biomarkers are officially here to stay in gastrointestinal oncology.⁴

References

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