HER2 testing and trastuzumab in advanced gastric and gastroesophageal cancer

HOT SPOT

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Background

- Herceptin® approved by Health Canada for first-line treatment of patients with HER2 positive metastatic adenocarcinoma of stomach or gastroesophageal cancer in combination with cisplatin and capecitabine or fluorouracil.

HER2 expression in gastric cancer

- HER2 over-expression/amplification occurs in 16% to 22% of gastric adenocarcinoma and in gastroesophageal junction cancer, and is more common in tumours of the intestinal subtype (Bang et al., 2010; Tanner et al., 2005; Hoffman et al., 2008; Ruschoff et al., 2010).
- HER2 testing methodologies are similar to those in breast cancer, but interpretation and scoring guidelines differ significantly (Hoffman et al., 2008; Ruschoff et al., 2010).
- Any pathology laboratory performing this test in GC/GEJC must be using appropriate site-specific guidelines.
- Inappropriate use of breast cancer criteria will underestimate true HER2 positivity rates in GC/GEJC, which exhibits greater tumour heterogeneity for HER2 expression.

HER2 testing

- The two validated and complementary methods used for HER2 testing are immunohistochemistry (IHC) and in situ hybridization (ISH), the latter either fluorescence-based (FISH) or silver-based (SISH).
- Testing can be performed on formalin-fixed, paraffin embedded tumour tissue, making it unnecessary to obtain fresh tissue.
- Any tumour-rich block from a resection specimen or a generous biopsy specimen can be used for analysis.
- For biopsies, endoscopists and interventional radiologists, etc., are encouraged to provide samples of preferably six or more biopsy fragments in order to reduce false negative results due to sampling error and intratumoural heterogeneity.

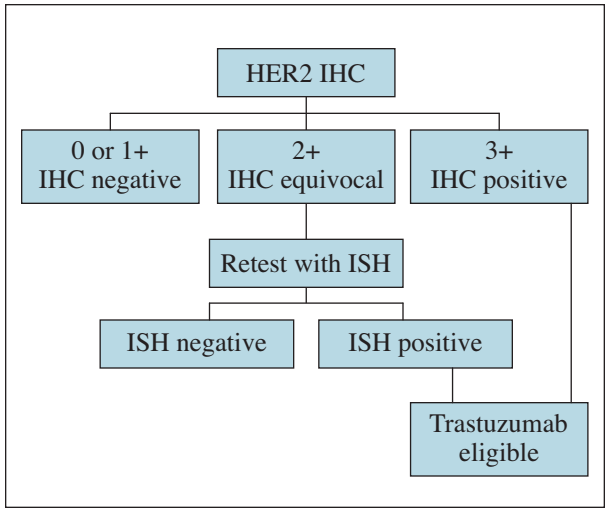

Figure 1: Patients are eligible for trastuzumab if the tumour is 3+ by IHC or has 2+ IHC & ISH amplification

HER2 grading in gastric cancer

- The recommended protocol begins with IHC, with additional testing of equivocal IHC cases by FISH or SISH.
- On a scale of 0 to 3, samples that show 3+ IHC staining are considered HER2 positive, and those that show 0 or 1+ staining are considered negative.
- Those with 2+ IHC expression should be retested by ISH.

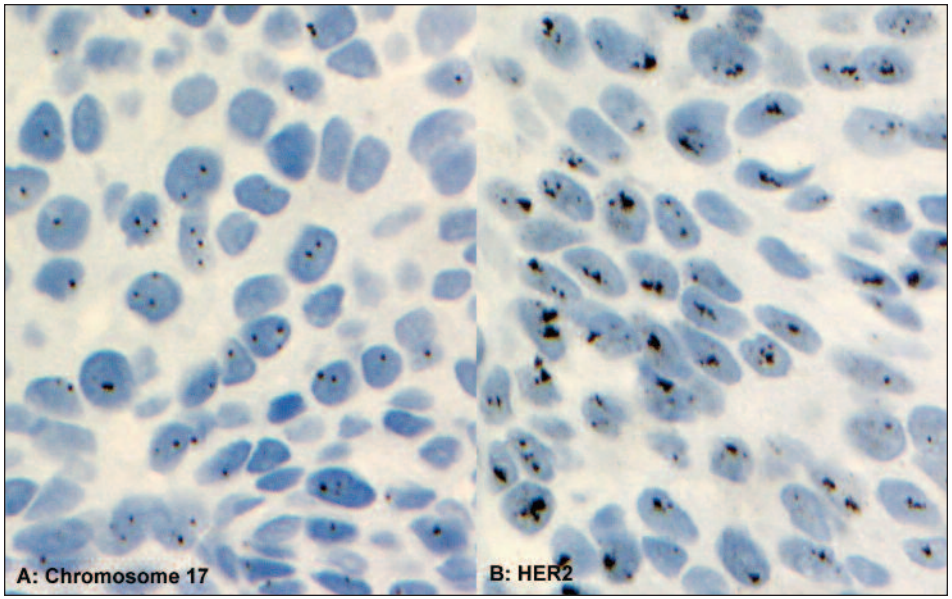

Figure 2: A. Chr. 17 SISH demonstrates 1–3 chromosomal copies per tumour cell B. HER2 SISH shows numerous copies per cell with signal clustering, indicative of HER2 gene amplification

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Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer: ToGA Study

Study design

- International multi-centre, open-label, randomized study.
- 1:1 randomization stratified by performance status, extent of disease, primary site, chemotherapy regimen and disease measurability.
- Primary endpoint was overall survival assuming an improvement in overall survival from 10 to 13 months.

Inclusion criteria

- Histologically confirmed adenocarcinoma of the stomach or gastro-esophageal junction that was metastatic or locally inoperable.
- ECOG performance status of 0 to 2.
- Tumours were centrally tested for HER2 with immunohistochemistry (IHC)(HercepTest) and fluorescence in-situ hybridization (FISH;HER FISH pharmDx) based on modified scoring criteria. Tumours were considered positive if they were FISH positive (HER2:CEP17≥2) or 3+ on immunohistochemistry.

Treatment

- Chemotherapy given every three weeks for six cycles.
- Capecitabine was given at 1000 mg/m^2 twice a day for 14 days or fluorouracil 800 mg/m^2 per day by continuous infusion on days one to five of each cycle.
- Cisplatin was given at 80 mg/m^2 on day one.
- Trastuzumab was given at 8 mg/kg on day 1 and continued until progression, toxicity or withdrawal.

	Trastuzumab Arm	Chemotherapy Arm	P-value
Overall Survival	13.8 months	11.1 months	0.0046
Progression Free Survival	6.7 months	5.5 months	0.0002
Time to Progression	7.1 months	5.6 months	0.0003
Duration of Response	6.9 months	4.8 months	<0.0001
Overall Response Rate	47%	35%	0.0017
Stable Response Rate	32%	35%	NS

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Results

- 3,803 patients assessed and 3,665 screened for HER2 by IHC or FISH.
- 810 HER2 positive, but 216 failed at least one entry criterion.
- 594 randomized to treatment (four did not receive treatment on study arm and six did not receive treatment on control arm).
- Majority of patients received capecitabine.
- Median number of trastuzumab was eight (1 – 49).
- More than 40% of patients received second line chemotherapy.

Toxicity

- Slightly higher rate of diarrhea, stomatitis, anemia, thrombocytopenia, fatigue, chills, weight loss, fever, nasopharyngitis in trastuzumab group.
- Severe infusion reactions in 6% of patients receiving trastuzumab.
- No difference in cardiac events (6%).

Commentary

- Encouraging response rates and improvement in overall survival, especially in those who have tumours that are IHC 3+ and ISH+.
- Only minority of patients over-express HER2.
- Cross trial comparison to REAL-2 (Cunningham et al.) difficult due to difference in chemotherapy drugs and doses.
- Unknown benefits of going beyond six cycles of chemotherapy.
- Cannot determine contribution of continued trastuzumab (continued in ToGA study until progression) versus stopping trastuzumab at time of chemotherapy completion (at six cycles).

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