

Chapter4

Slide 1

Next, I will talk about genomic medicine for breast cancer.

Based on expression of the estrogen receptor and the progesterone receptor (hormone receptors) and HER2, breast cancer is categorized as shown in this table.

In routine clinical practice, expression of a hormone receptor is detected using immunostaining, but expression of HER2 is detected via gene amplification with FISH in addition to immunostaining.

In other words, this falls under genomic medicine, as I will explain.

The HER2 gene is amplified in around 20% of patients with breast cancer.

Slide 2

HER2 is an abbreviation for human epidermal growth factor receptor 2.

HER2 is also called erbB2 or neu.

As its name indicates, HER2 is a receptor tyrosine kinase belonging to the EGFR family. The gene is encoded on the long arm of chromosome 17.

HER2 is thought to be associated with the development and maintenance of the heart and nerves, but there are no known ligands that bind to HER2.

HER2 forms a homodimer, in which HER2 binds to HER2, or a heterodimer, in which HER2 binds to another protein in the EGFR family, facilitating signaling downstream.

When the HER2 is amplified, HER2 protein is overexpressed. Overexpressed HER2 protein facilitates growth signaling, and breast cancer grows.

Slide 3

There are 2 methods of assessing HER2 amplification: immunostaining and FISH. In immunostaining, the intensity with which the cell membrane of tumor cells is stained is assessed and scored.

In FISH, 20 tumor cells are assessed, and the ratio of HER2 signaling to endogenous control signaling is calculated. If the ratio is greater than 2.2, then the HER2 gene is deemed to be amplified.

Slide 4

If immunostaining reveals the staining of the cell membrane of more than 30% of invasive cancer cells with an even intensity, then a score of 3+ is given. If only immunostaining is performed, administration of Herceptin (trastuzumab) is indicated. If staining is weaker (a score of 2+), then FISH is performed. If the HER2/CEP17 ratio is $2.2 \geq$, then the gene is amplified and Herceptin is indicated.

Slide 5

The efficacy of trastuzumab, an anti-HER2 antibody, is correlated with HER2 expression by breast cancer cells.

The response rate to trastuzumab alone is around 5% in patients who test negative according to FISH but 35% in patients with a score of 3+ in immunostaining or who test positive according to FISH.

In addition, adding trastuzumab to an anticancer agent to treat HER2-expressing breast cancer significantly increased the progression-free survival rate compared to an anticancer agent alone.

Thus, breast cancer highly expressing HER2 is identified and genomic medicine is provided in the form of personalized medicine using an anti-HER2 antibody.

Slide 6

Personalized medicine is similarly provided to treat expression of HER2 in gastric cancer.

Gastric cancer is categorized as an intestinal type or a diffuse/mixed type based on mucin expression. Overexpression of HER2 is noted at a frequency of 15–50% in the intestinal type and 2–25% in the diffuse/mixed type.

HER2 expression in gastric cancer, like that in breast cancer, is detected using immunostaining and ISH. If immunostaining yields a score of 3+, then an anti-HER2 molecularly targeted therapy is indicated. If the score is 2+, then the specimen is retested using ISH. Caution is required since the cutoff for positivity according to ISH is 2.0, unlike the cutoff of 2.2 for breast cancer. If results are positive according to ISH, then anti-HER2 molecularly targeted therapy is indicated.

Slide 7

Here are images obtained using immunostaining (immunohistochemistry or IHC) and dual color in situ hybridization (DISH) to test actual gastric cancer tissue for HER2 expression.

Immunostaining revealed a high level of HER2 protein expression on the cell membrane in gastric cancer tissue on the left and DISH revealed HER2 gene amplification in the nucleus (black dots), so the HER2 gene was amplified from cancer cells at those sites, and the HER2 protein was overexpressed.

Immunostaining and DISH revealed no expression of the HER2 protein or gene in the gastric cancer tissue on the right.

In other words, HER2 expression in gastric cancer can be assessed using immunostaining and ISH. With HER2-positive breast cancer, almost every cancer cell will test positive, but heterogeneity in HER2 expression will be present in gastric cancer, so caution is required. If @@% of cells are positive, then the patient is diagnosed with HER2-positive gastric cancer, and therapy targeting HER2 is indicated.

Slide 8

Shown here are the standards for detecting HER2 with immunostaining.

Slide 9

Here are the results of the ToGA trial, which compared the efficacy of standard chemotherapy as initial treatment of HER2-positive advanced gastric cancer and a combination of trastuzumab (an anti-HER2 antibody) and standard chemotherapy. A group receiving cisplatin+5FU as standard chemotherapy had a median survival of 11.1 months while a group receiving trastuzumab in addition to cisplatin+5FU had a median survival of 13.8 months, so median survival was prolonged 2.7 months. Based on a hazard ratio of 0.74 and significant differences as indicated by a P value of 0.0046, results indicated that trastuzumab should be added.

Thus, HER2 expression and gene amplification are assessed in breast cancer as well as gastric cancer, and genomic medicine is provided in the form of personalized medicine.