Difficulties in Developing HER2-Targeted Therapy for Gastric Cancer

Subjects: Oncology

Contributor: Shin Ariga

Advances in novel drugs and sequencing technologies have made biomarker-based, personalized, and effective treatment options available for patients with various types of solid tumor. Biomarker-based targeted therapy has dramatically changed the treatment of various cancers, such as non-small cell lung cancer. The first biomarker to be developed as a therapeutic target in gastric adenocarcinoma and gastroesophageal junction adenocarcinoma (hereafter, gastric cancer) was human epidermal growth factor 2 (HER2). Human epidermal growth factor receptor 2 (HER2) is a receptor tyrosine kinase that belongs to the human epidermal growth factor receptor family. It is overexpressed/amplified in approximately 20% of gastric or gastroesophageal junction cancers. HER2 is being developed as a therapeutic target in a variety of cancers, and several agents have been shown to be effective in breast cancer.

gastric cancer HER2 targeted therapy heterogeneity

1. Introduction

HER2 belongs to the human epidermal growth factor receptor (EGFR) family of tyrosine kinase receptors. HER2 has no activating ligand but can undergo dimerization with EGFR family members to activate multiple downstream signaling pathways, including the RAS/RAF/MAPK and PI3K/AKT cascades [1]. The extracellular domain of HER2 consists of four subdomains (I–IV), including domain II, the so-called dimerization domain, which is essential for ligand-induced heterodimerization.

The frequency of HER2 overexpression/amplification in gastric cancer is approximately 20% [2]. HER2 positivity is more common in gastroesophageal cancer as the primary site, and more common in intestinal-type tumors pathologically. However, the evaluation of HER2 as a prognostic factor remains controversial [3]. Although the efficacy of HER2-targeted therapies has been successfully demonstrated in breast cancer with HER2 overexpression/amplification, the development of HER2-targeted therapy for gastric cancer has not gone smoothly.

After the ToGA study, HER2-targeted drugs that are effective for breast cancer successively failed to show survival benefits in gastric cancer. There are clear differences between breast cancer and gastric cancer in HER2-targeted therapy, and hence there are several possible causes of the ineffectiveness of HER2-targeted therapy against gastric cancer.

2. HER2 Heterogeneity in Gastric Cancer

The most likely reason for HER2 therapy ineffectiveness is the heterogeneity of HER2 overexpression and/or amplification, which many authors highlighted in the discussion sections of their papers [4][5][6]. Generally, one mechanism of resistance to targeted therapy is the heterogeneous expression of the therapeutic target within the tumor [7]. Even in breast cancer, heterogeneous HER2 expression is well known [8] and definitions for HER2 heterogeneity are proposed in the guidelines [9][10]. However, in gastric cancer, the HER2 expression pattern confirmed by IHC is fundamentally heterogeneous and that is why the IHC assessment of HER2 in gastric cancer was changed from breast cancer in the ToGA study and subsequent studies. The results of the quantitative proteomic analysis indicated that the expression levels of the HER2 protein in gastric cancer exhibited significant variation, and in some cases, the levels were undetectable even in tissue samples exhibiting IHC 3+ positivity [11].

HER2 signal dependency may differ between breast cancer and gastric cancer. Breast cancer is classified into six intrinsic molecular subtypes based on gene expression profiles, and the “HER2-enriched” subtype is independent as one of these subtypes [12][13]. Gastric cancer has also been classified into molecular subtypes via comprehensive analysis. Two representative classifications were reported by the Cancer Genome Atlas (TCGA) and the Asian Cancer Research Group (ACRG) [14][15]. TCGA proposed four principal molecular subgroups of gastric cancer: the microsatellite instable (MSI), Epstein–Barr virus (EBV)-associated, chromosomally instable (CIN), and genomically stable groups. Similarly, the ACRG divided gastric cancer into four subtypes: MSI, microsatellite stable (MSS)/*TP53* active, MSS/*TP53* inactive, and MSS/mesenchymal-like. Of note, neither classification independently categorized the “HER2-enriched” subtype. Interestingly, in TCGA classification, HER2 amplification is mainly associated with the CIN subgroup; however, other receptor tyrosine kinase alterations are also included in the same subgroup and partially overlap. Additionally, the EBV subgroup also includes HER2 amplification. These data indicated that in gastric cancer, HER2 alterations are molecularly heterogenous and might not be the independent oncogenic driver; that is, blocking the HER2 pathway might not be enough to kill cancer cells. Thus, HER2-targeted therapy for gastric cancer may require more than just blocking the HER2 pathway.

3. Definition of HER2-Positive Gastric Cancer

The “HER2-positive” definition is another discussion point. For some other biomarkers for targeted therapies, for instance “EGFR-positive” lung cancer, it is relatively easy to distinguish positive from negative according to whether there is an active *EGFR* gene mutation. Additionally, the effect of EGFR tyrosine kinase inhibitors is clearly different between “EGFR-positive” and “EGFR-negative” lung cancer [16].

However, HER2 is more complicated. HER2 expression has been used as a predictive biomarker of HER2-targeted therapy, but the degree of HER2 expression widely varies from no expression to high expression. In an early clinical trial of trastuzumab against breast cancer, HER2 expression was regarded as positive when more than 25% of tumor cells exhibited characteristic membrane staining for HER2 [17]. In the pivotal phase 2 single-agent and phase 3 combination studies of trastuzumab against breast cancer [18][19], the IHC scoring system was more organized in relation to the HER2 receptor number (no staining (score 0), <20,000 receptors; partial membrane staining with <10% of the cells showing complete membrane staining (score 1+), 100,000 receptors;

light to moderate complete membrane staining in >10% of the cells (score 2+), 500,000 receptors; and complete membrane staining in >10% of the cells (score 3+), 2,300,000 receptors) [20]. In these two pivotal studies, HER2 IHC 2+ and 3+ were regarded as “HER2-positive”, but this cutoff was based on biological features, and the results of the studies indicated that patients with a HER2 score of 3+ would gain more benefit from trastuzumab [21]. Therefore, a subsequent study adopted HER2 IHC 3+ as the definition of “HER2-positive” breast cancer [22]. However, these and other data also indicated that trastuzumab had a slight effect against HER2 IHC 2+ breast cancer even though HER2 FISH was negative (HER2:CEP17 ratio < 2.0) [23]. Additionally, recent studies have shown that the intrinsic phenotypes of HER2 IHC 1+/2+ breast cancer overlap among luminal A/B, basal-like, normal-like, and HER2-enriched types [24][25]. The trastuzumab biomarkers of breast cancer would be continuous rather than categorical or binary, and this may be partially independent of genetic phenotypes. Namely, when HER2 expression/amplification is above the artificial cutoff regarding the clinically acceptable benefits of trastuzumab, it is described as “HER2-positive” breast cancer.

From this point of view, the “HER2-positive” definition should vary for each drug, as diverse HER2-targeted therapies necessitate distinct HER2 statuses to attain efficacy. Fortunately, in breast cancer, HER2-targeted therapies have the same “HER2-positive” definition as trastuzumab, but it might be different in gastric cancer. For instance, even though T-DM1 failed to show clinical benefits in ToGA study-based HER2-positive gastric cancer compared with taxane, it seemed that HER2 expression was a predictive biomarker for T-DM1 against gastric cancer [5]. If the cutoff value for HER2 positivity due to HER2 protein levels was set higher, T-DM1 might have demonstrated clinical benefits (however, this is not realistic because of the small number of applicable patients or technical/cost aspects regarding quantifying the amount of protein).

4. Racial Specificity of Gastric Cancer

Regional differences in gastric cancer are not a major problem but should be noted. Gastric cancer in Asia and the West are biologically different with respect to incidence, etiology, tumor location, and clinicopathological characteristics [26][27]. Asia and the West also have clinical differences with regard to the screening protocols used or treatment modalities, such as surgical approaches or perioperative treatment [28]. Generally, Asian patients tend to have a better prognosis than Western patients [29][30], but it may be a chicken and egg scenario; Asia, especially Japan, tends to use more lines of chemotherapy than the West [31]. These differences complicate the interpretation of the results of global gastric cancer clinical trials.

The AVAGAST study was a global phase 3 study that aimed to evaluate the efficacy of another molecular targeted drug, bevacizumab, against gastric cancer following the ToGA study [32]. Although this study did not show an overall improvement in survival in the whole population, a subgroup analysis indicated that Western patients tended to have a prolonged median overall survival when bevacizumab was added to chemotherapy (11.5 months vs. 6.8 months, hazard ratio 0.63 in Pan America; and 11.1 months vs. 8.6 months, hazard ratio 0.85 in Europe). Conversely, in Asia, the addition of bevacizumab appeared to have no effect on the median overall survival (13.9 months vs. 12.1 months, hazard ratio 0.97). Notably, the numerical median overall survival of Asian patients without bevacizumab was longer than that of Western patients with bevacizumab. Researchers pointed out that the

difference in the use of the post-progression chemotherapy rate (68% in Asia and 23% other region) was one of the factors that contributed to the different survival outcomes between regions [33]. Even the ToGA study identified similar trends [34]. A subgroup analysis showed that the numerical median overall survival was not different with or without trastuzumab in Japanese patients (15.9 months for trastuzumab plus chemotherapy arm and 17.7 months for chemotherapy arm, hazard ratio 1.00) and that both were longer than the trastuzumab plus chemotherapy arm in the overall population (13·8 months). In the ToGA study, 80.4% in the trastuzumab plus chemotherapy arm and 82% in the chemotherapy arm in Japanese patients received second-line treatment, whereas only 42% in the trastuzumab plus chemotherapy arm and 45% in the chemotherapy arm in the overall population received second-line treatment. Intensive treatment and a long survival in Asia could mitigate the benefits of a new drug in clinical studies, especially in the first-line setting. These trends could also be seen in the latest global phase 3 studies of the PD-1-blocking antibody nivolumab for gastric cancer by comparing Checkmate 649, which was conducted mainly outside of Asia, with the ATTRACTION-4 study, which was conducted in East Asia [35][36][37]. In other words, very powerful HER2-targeted therapy is required to demonstrate a statistically significant overall survival in HER2-positive gastric cancer clinical studies, including in Asia.

In summary, to demonstrate the survival benefits of HER2-targeted therapy for gastric cancer, a drug is required that targets beyond the HER2 pathway-blocking mechanisms and has strong anti-tumor effects, especially for Asian patients, with an appropriate predictive biomarker (“HER2-positive” definition). Recently, a new drug, trastuzumab deruxtecan, has emerged that meets some of these requirements.

References

1. Yarden, Y.; Sliwkowski, M.X. Untangling the ErbB signalling network. Nat. Rev. Mol. Cell Biol. 2001, 2, 127–137.
2. Van Cutsem, E.; Bang, Y.J.; Feng-Yi, F.; Xu, J.M.; Lee, K.W.; Jiao, S.C.; Chong, J.L.; López-Sanchez, R.I.; Price, T.; Gladkov, O.; et al. HER2 screening data from ToGA: Targeting HER2 in gastric and gastroesophageal junction cancer. Gastric Cancer 2015, 18, 476–484.
3. Gravalos, C.; Jimeno, A. HER2 in gastric cancer: A new prognostic factor and a novel therapeutic target. Ann. Oncol. 2008, 19, 1523–1529.
4. Bang, Y.-J.; Van Cutsem, E.; Feyereislova, A.; Chung, H.C.; Shen, L.; Sawaki, A.; Lordick, F.; Ohtsu, A.; Omuro, Y.; Satoh, T.; et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 2010, 376, 687–697.
5. Thuss-Patience, P.C.; Shah, M.A.; Ohtsu, A.; Van Cutsem, E.; Ajani, J.A.; Castro, H.; Mansoor, W.; Chung, H.C.; Bodoky, G.; Shitara, K.; et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal

junction adenocarcinoma (GATSBY): An international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncol. 2017, 18, 640–653.

6. Tabernero, J.; Hoff, P.M.; Shen, L.; Ohtsu, A.; Shah, M.A.; Cheng, K.; Song, C.; Wu, H.; Eng-Wong, J.; Kim, K.; et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): Final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2018, 19, 1372–1384.
7. Marusyk, A.; Janiszewska, M.; Polyak, K. Intratumor Heterogeneity: The Rosetta Stone of Therapy Resistance. Cancer Cell 2020, 37, 471–484.
8. Hanna, W.M.; Rüschoff, J.; Bilous, M.; Coudry, R.A.; Dowsett, M.; Osamura, R.Y.; Penault-Llorca, F.; van de Vijver, M.; Viale, G. HER2 in situ hybridization in breast cancer: Clinical implications of polysomy 17 and genetic heterogeneity. Mod. Pathol. 2014, 27, 4–18.
9. Vance, G.H.; Barry, T.S.; Bloom, K.J.; Fitzgibbons, P.L.; Hicks, D.G.; Jenkins, R.B.; Persons, D.L.; Tubbs, R.R.; Hammond, M.E. Genetic heterogeneity in HER2 testing in breast cancer: Panel summary and guidelines. Arch. Pathol. Lab. Med. 2009, 133, 611–612.
10. Bernasconi, B.; Chiaravalli, A.M.; Finzi, G.; Milani, K.; Tibiletti, M.G. Genetic heterogeneity in HER2 testing may influence therapy eligibility. Breast Cancer Res. Treat. 2012, 133, 161–168.
11. An, E.; Ock, C.Y.; Kim, T.Y.; Lee, K.H.; Han, S.W.; Im, S.A.; Kim, T.Y.; Liao, W.L.; Cecchi, F.; Blackler, A.; et al. Quantitative proteomic analysis of HER2 expression in the selection of gastric cancer patients for trastuzumab treatment. Ann. Oncol. 2017, 28, 110–115.
12. Perou, C.M.; Sørlie, T.; Eisen, M.B.; van de Rijn, M.; Jeffrey, S.S.; Rees, C.A.; Pollack, J.R.; Ross, D.T.; Johnsen, H.; Akslen, L.A.; et al. Molecular portraits of human breast tumours. Nature 2000, 406, 747–752.
13. Sørlie, T.; Perou, C.M.; Tibshirani, R.; Aas, T.; Geisler, S.; Johnsen, H.; Hastie, T.; Eisen, M.B.; van de Rijn, M.; Jeffrey, S.S.; et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc. Natl. Acad. Sci. USA 2001, 98, 10869–10874.
14. The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014, 513, 202–209.
15. Cristescu, R.; Lee, J.; Nebozhyn, M.; Kim, K.M.; Ting, J.C.; Wong, S.S.; Liu, J.; Yue, Y.G.; Wang, J.; Yu, K.; et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat. Med. 2015, 21, 449–456.
16. Mok, T.S.; Wu, Y.L.; Thongprasert, S.; Yang, C.H.; Chu, D.T.; Saijo, N.; Sunpaweravong, P.; Han, B.; Margono, B.; Ichinose, Y.; et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N. Engl. J. Med. 2009, 361, 947–957.

17. Baselga, J.; Tripathy, D.; Mendelsohn, J.; Baughman, S.; Benz, C.C.; Dantis, L.; Sklarin, N.T.; Seidman, A.D.; Hudis, C.A.; Moore, J.; et al. Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. J. Clin. Oncol. 1996, 14, 737–744.
18. Slamon, D.J.; Leyland-Jones, B.; Shak, S.; Fuchs, H.; Paton, V.; Bajamonde, A.; Fleming, T.; Eiermann, W.; Wolter, J.; Pegram, M.; et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N. Engl. J. Med. 2001, 344, 783–792.
19. Cobleigh, M.A.; Vogel, C.L.; Tripathy, D.; Robert, N.J.; Scholl, S.; Fehrenbacher, L.; Wolter, J.M.; Paton, V.; Shak, S.; Lieberman, G.; et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J. Clin. Oncol. 1999, 17, 2639–2648.
20. Ross, J.S.; Slodkowska, E.A.; Symmans, W.F.; Pusztai, L.; Ravdin, P.M.; Hortobagyi, G.N. The HER-2 receptor and breast cancer: Ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 2009, 14, 320–368.
21. Baselga, J. Herceptin alone or in combination with chemotherapy in the treatment of HER2-positive metastatic breast cancer: Pivotal trials. Oncology 2001, 61 (Suppl. S2), 14–21.
22. Marty, M.; Cognetti, F.; Maraninchi, D.; Snyder, R.; Mauriac, L.; Tubiana-Hulin, M.; Chan, S.; Grimes, D.; Antón, A.; Lluch, A.; et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: The M77001 study group. J. Clin. Oncol. 2005, 23, 4265–4274.
23. Mass, R.D.; Press, M.F.; Anderson, S.; Cobleigh, M.A.; Vogel, C.L.; Dybdal, N.; Leiberman, G.; Slamon, D.J. Evaluation of clinical outcomes according to HER2 detection by fluorescence in situ hybridization in women with metastatic breast cancer treated with trastuzumab. Clin. Breast Cancer 2005, 6, 240–246.
24. Schettini, F.; Chic, N.; Brasó-Maristany, F.; Paré, L.; Pascual, T.; Conte, B.; Martínez-Sáez, O.; Adamo, B.; Vidal, M.; Barnadas, E.; et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. NPJ Breast Cancer 2021, 7, 1.
25. Agostinetto, E.; Rediti, M.; Fimereli, D.; Debien, V.; Piccart, M.; Aftimos, P.; Sotiriou, C.; de Azambuja, E. HER2-Low Breast Cancer: Molecular Characteristics and Prognosis. Cancers 2021, 13, 2824.
26. Davis, P.A.; Sano, T. The difference in gastric cancer between Japan, USA and Europe: What are the facts? what are the suggestions? Crit. Rev. Oncol. Hematol. 2001, 40, 77–94.

27. Shim, J.H.; Song, K.Y.; Jeon, H.M.; Park, C.H.; Jacks, L.M.; Gonen, M.; Shah, M.A.; Brennan, M.F.; Coit, D.G.; Strong, V.E. Is gastric cancer different in Korea and the United States? Impact of tumor location on prognosis. Ann. Surg. Oncol. 2014, 21, 2332–2339.
28. Russo, A.E.; Strong, V.E. Gastric Cancer Etiology and Management in Asia and the West. Annu. Rev. Med. 2019, 70, 353–367.
29. Zhang, Z.; Liu, Z.; Chen, Z. Comparison of Treatment Efficacy and Survival Outcomes Between Asian and Western Patients with Unresectable Gastric or Gastro-Esophageal Adenocarcinoma: A Systematic Review and Meta-Analysis. Front. Oncol. 2022, 12, 831207.
30. Jin, H.; Pinheiro, P.S.; Callahan, K.E.; Altekruse, S.F. Examining the gastric cancer survival gap between Asians and whites in the United States. Gastric Cancer 2017, 20, 573–582.
31. Komatsu, Y.; Hironaka, S.; Tanizawa, Y.; Cai, Z.; Piao, Y.; Boku, N. Treatment Pattern for Advanced Gastric Cancer in Japan and Factors Associated with Sequential Treatment: A Retrospective Administrative Claims Database Study. Adv. Ther. 2022, 39, 296–313.
32. Ohtsu, A.; Shah, M.A.; Van Cutsem, E.; Rha, S.Y.; Sawaki, A.; Park, S.R.; Lim, H.Y.; Yamada, Y.; Wu, J.; Langer, B.; et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: A randomized, double-blind, placebo-controlled phase III study. J. Clin. Oncol. 2011, 29, 3968–3976.
33. Sawaki, A.; Yamada, Y.; Yamaguchi, K.; Nishina, T.; Doi, T.; Satoh, T.; Chin, K.; Boku, N.; Omuro, Y.; Komatsu, Y.; et al. Regional differences in advanced gastric cancer: Exploratory analyses of the AVAGAST placebo arm. Gastric Cancer 2018, 21, 429–438.
34. Sawaki, A.; Ohashi, Y.; Omuro, Y.; Satoh, T.; Hamamoto, Y.; Boku, N.; Miyata, Y.; Takiuchi, H.; Yamaguchi, K.; Sasaki, Y.; et al. Efficacy of trastuzumab in Japanese patients with HER2-positive advanced gastric or gastroesophageal junction cancer: A subgroup analysis of the Trastuzumab for Gastric Cancer (ToGA) study. Gastric Cancer 2012, 15, 313–322.
35. Janjigian, Y.Y.; Shitara, K.; Moehler, M.; Garrido, M.; Salman, P.; Shen, L.; Wyrwicz, L.; Yamaguchi, K.; Skoczylas, T.; Campos Bragagnoli, A.; et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): A randomised, open-label, phase 3 trial. Lancet 2021, 398, 27–40.
36. Shitara, K.; Ajani, J.A.; Moehler, M.; Garrido, M.; Gallardo, C.; Shen, L.; Yamaguchi, K.; Wyrwicz, L.; Skoczylas, T.; Bragagnoli, A.C.; et al. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. Nature 2022, 603, 942–948.
37. Kang, Y.K.; Chen, L.T.; Ryu, M.H.; Oh, D.Y.; Oh, S.C.; Chung, H.C.; Lee, K.W.; Omori, T.; Shitara, K.; Sakuramoto, S.; et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-

oesophageal junction cancer (ATTRACTION-4): A randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2022, 23, 234–247.