

Targeting of HER Family Signaling Pathways in Gastric Cancer

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Gastric Cancer

Gastric cancer is the fourth most common malignant disease and the second leading cause of cancer mortality worldwide [1]. In 2008, an estimated 989,000 new cases were reported according to the International Agency for Research on Cancer [1,2]. Unfortunately, due to the vague and unspecific symptoms of this malignancy, many patients do not present for evaluation in its early stages. At time of diagnosis, most gastric cancer patients present with metastatic disease, and the median survival is eight to ten months [3]. Gastric cancer, although a disease of the developing countries, has become one of the most rapid growing cancers in many parts of the world, with incidence rising five- to six-fold over the past 30 years in developed nations [4-10]. As this malignancy has a high mortality rate, large efforts are underway to investigate targeted therapies that slow progression, metastasis, and decrease mortality. Biomarker directed therapies have made great strides in cancers such as melanoma, colorectal and breast cancer, and there is an urgent need to examine the utility of biomarkers in the treatment of gastric cancer.

HER2 Tyrosine Kinase Receptor and ToGA Trial

One study in particular, the ToGA trial (Trastuzumab for Gastric Cancer), demonstrated how knowledge of membrane receptors and their signaling cascade in cells can be utilized to find targeted therapy [11]. The agent studied, trastuzumab, is a recombinant humanized monoclonal antibody that targets the extracellular domain IV of the human epidermal growth receptor 2 (HER2) tyrosine kinase receptor [12]. It functions to regulate imperative cellular activity including growth, differentiation, and apoptosis [12]. This is significant as HER2 is overexpressed in 10-30% of gastric cancers [13], making HER2 a potential biomarker for the treatment of gastric cancer.

ToGA was an open-label, phase 3, randomized controlled trial evaluated in 122 centers among 24 countries. The trial consisted of two treatment arms that evaluated chemotherapy in conjunction with trastuzumab, or chemotherapy alone to determine efficacy of trastuzumab as a treatment option for HER2 positive gastric and gastro-esophageal junction cancers [14,15]. A total of 584 patients were randomized to receive fluoropyrimidine + cisplatin + trastuzumab or fluoropyrimidine + cisplatin. The median Overall Survival (OS) of the trastuzumab group was 13.8 months compared to 11.1 months in the chemo only group, corresponding with an impressive reduced risk of death by 26%. This trial supported trastuzumab as an effective targeted agent for HER2 positive gastric cancer, providing the rationale for a closer look at the HER family and its function in gastric cancer.

HER Family Receptors and Gastric Cancer

HER family contains tyrosine kinase receptors that include HER1 (EGFR), HER2, HER3, and HER4 [16]. When these receptors are activated, phosphorylation of downstream pathways is initiated. Two pathways are of particular interest: the Phosphatidylinositol-3-kinase (PI3K)/Akt and the Mitogen-activated protein kinase (MAPK)/Ras pathways. When they are activated, there is an increased risk for multidrug resistance and metastasis. This concept of multi-drug

resistance was demonstrated using MCF7 breast cancer cells; when MCF7 cells were engineered to express elevated levels of HER2, a PI3K-dependent increase in Akt activity led to resistance of five chemotherapy agents with different mechanisms of action [17]. In this study, not only elevated levels, but also constitutive action of Akt increased multi-drug resistance. This pathway's association with metastasis was evaluated via an *in vitro* study of human gastric cancer cell lines GLM-1, GLM-2, and GLM-4. This study demonstrated that a higher percentage of HER2 overexpressing cells was present in liver metastasis from gastric cancer compared to the primary tumor [18], suggesting that HER2 overexpression could be related to liver metastasis in gastric cancer. CXCR4 is another downstream receptor of HER2; it is associated with metastasis [19]. Most breast cancer cells that overexpress HER2 also express CXCR4, which is regulated through the PI3K/Akt pathway [19-21]. In a study to evaluate how HER2 overexpression increased metastatic potential, CXCR4 was shown to be required for HER2-mediated metastatic potential in breast cancer *in vitro* and *in vivo* models [19]. HER2 is unique, as it does not require a ligand for activation; in fact it can homodimerize (bind to another HER2) or heterodimerize (bind to another her family receptor such as HER3) [22]. Such unique feature of HER2 activation leads itself to additional pathways which may help its activity and antibody against only the HER2 receptor may not offer the most optimal treatment strategy for HER2 positive gastric cancer.

HER2 is not the only tyrosine kinase receptor that is overexpressed in gastric cancer. The different histological types of gastric cancer such as intestinal and diffuse types have been shown to overexpress both HER2 and HER3 [23]. Intestinal type has predominance of HER2 overexpression over HER3, while diffuse type has increased overexpression of HER3 compared to HER2 [23]. In a study where gastrectomy samples were obtained from 134 patients with gastric adenocarcinomas, HER3 overexpression was significantly correlated with increased depth of tumor invasion, involved lymph nodes, distant metastasis, more advanced tumor stage, and increase in recurrent disease [24]. HER3 overexpression served as a poor prognostic factor in this study. In another study that evaluated gastric cancer tissues from patients who underwent curative surgery, it was noted that when EGFR and HER2 receptors were blocked, HER3 activity was upregulated [23]. The role of HER3 in the progression of malignancy has also been tested in breast cancer. HER3 inhibition in HER2 overexpressing breast

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cancer induced tumor regression in xenografts, leading to the notion of HER3 activity as a potential for trastuzumab resistance [25,26]. Such revelation has led to the development of agents that simultaneously target multiple binding receptors including EGFR, HER2, and HER3 to overcome trastuzumab resistance.

Trastuzumab Resistance and Other Therapy Options Targeting HER Family

Blocking other HER family receptors while simultaneously targeting HER2 with trastuzumab has also served as a modality to overcome resistance seen with trastuzumab treatment for breast cancer. Pertuzumab is a FDA-approved agent for HER2 positive breast cancer [27]. It is a humanized HER2 monoclonal antibody that inhibits signaling from HER2/HER3 and HER2/EGFR heterodimers [28]. When used in conjunction with trastuzumab and chemotherapy, the synergistic activity of binding both HER2/HER3 or HER2/HER1 was thought to overcome resistance only when trastuzumab was bound to HER2 [29]. The therapeutic success of pertuzumab in metastatic HER2 positive breast cancer with increased response rate and progression free survival provides hope for HER2 positive gastric cancer using a similar approach.

This synergistic activity is also exemplified with the agent lapatinib, a small tyrosine kinase inhibitor that has activity in combination with trastuzumab for HER2 + breast cancer that progressed through two lines of trastuzumab related therapies [30]. Its activity is found at both HER2 and EGFR, and it could inhibit HER2 and EGFR dependent activation of PI3K/Akt and Ras/MAPK pathways, causing prolonged downregulation of receptor tyrosine phosphorylation in tumor cells [30]; with the ultimate goal to induce growth arrest and apoptosis [32]. Compared to monotherapy capecitabine, the combination of lapatinib and capecitabine increased the time to progression after patients progressed on trastuzumab-based treatment in metastatic HER2 positive breast cancer [32]. The median time to progression was 8.4 months in the combination-therapy group compared to 4.4 months in the monotherapy group. In addition, the study achieved an overall response rate of 22% in the combination group, compared to 14% in the monotherapy group [32]. Lapatinib is an attractive agent to test in HER2+ gastric cancer as it is administered orally with clinical activity in patients with HER2 positive metastatic breast cancer after trastuzumab failure.

Another potential mechanism of trastuzumab resistance arises at the level of HER2 downstream signals that are beyond PI3K/Akt and Ras/MAPK pathways, which ultimately deactivate p27^{Kip1}, a tumor suppressor protein [33,34]. This protein functions to promote cell-cycle arrest and apoptosis when activated, which can be initiated by the binding of trastuzumab to the HER2 receptor [35]. Cyclin-dependent kinase (CDK)2-mediated phosphorylation leads to degradation of p27^{Kip1} [36]. Trastuzumab increases the half-life of p27^{Kip1}, blocking CDK2-mediated phosphorylation and ultimately reduces the degradation of the protein [36]. This activity of trastuzumab leads to G1 cell-cycle arrest and reduction in tumor proliferation [37]. Trastuzumab resistant cells were noted to express decreased amount of p27^{Kip1} levels and increased CDK2 activity [38]. As a result, p27^{Kip1} level may be utilized as a marker of trastuzumab response and potential therapeutic target in trastuzumab-resistant gastric cancer. Thus, any agents that potentially suppress CDK2 function can be helpful in overcoming trastuzumab resistance. CDK2 inhibitors in early clinical development could be a therapeutic approach for HER2 + gastric cancer that have become resistant to trastuzumab. In addition, any

agents that potentially target upstream from the PI3K/Akt pathway, such as PI3K inhibitors, may be a potential solution for trastuzumab resistance in HER2 positive gastric cancer.

As the HER family receptors have been extensively evaluated, other receptors are currently under investigation as potential treatment against gastric cancer. New on the horizon, vascular endothelial growth factor receptor (VEGFR) inhibition, is providing possible new options.

New Appreciation for VEGF Inhibition

VEGFR -mediated signaling related to angiogenesis serves an important roles in the progression of gastric cancer [39], the activation of such receptor correlates with enhanced tumor activity. This recognition led to the development and administration of a novel drug in the treatment of gastric cancer.

Ramucirumab is a human IgG1 monoclonal antibody against VEGFR-2 that prevents binding of VEGFR-2 and its downstream pathway activation in endothelial cells [40]. It was studied in an international, randomized, double-blind, phase 3 trial at 119 centers in 29 countries [41]. Enrolled participants had advanced gastric or gastro-esophageal junction cancer with progression within 6 months of adjuvant therapy or progressed after first line treatment for metastatic disease. In a 2:1 randomized design, 238 patients were assigned to the ramucirumab group, and 117 to the placebo group. The treatment group had significant improvement in OS of 5.2 months compared to 3.8 months in the placebo group. The median PFS in the treatment group was 2.1 months compared to 1.3 months in those receiving placebo. The study supported the single agent activity of a VEGFR-2 inhibitor in advanced gastric and gastro-esophageal junction cancer.

The success with ramucirumab in gastric cancer poses new insights to further evaluate and appreciate the multiple receptors that actively lead to progression and metastasis of gastric cancer. Combining the activity of anti-HER2 agents and anti-angiogenesis agent in HER2 + gastric cancer is an attractive therapeutic approach. KD020 is an oral reversible tyrosine kinase inhibitor that targets multiple critical receptors: EGFR, HER2, VEGFR2/3, and Src [42]. The use of agents such as KD020 can serve as a new way of overcoming trastuzumab resistance in advanced gastric cancer.

Gastric cancer remains to be a malignancy with poor prognosis and survival at time of diagnosis, and it is imperative to implement aggressive treatment once diagnosis is confirmed. At this time, more understanding of the HER family receptors and beyond, together with further characterization of VEGF pathways in gastric cancer can lead to additional therapeutic options for this deadly disease.

Author Contribution

Dr. Perkins collected and analyzed the literature and prepared the manuscript

Dr. Wu formulated the concept, supervised the literature search, provided edits and gave final approval of the manuscript.

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