The human epidermal receptors in gastric cancer: molecular alterations and its role as therapeutic targets

Andrea Rebeca Bustos-Carpinteyro^{1,2}, María Teresa Magaña-Torres¹, Juan Ramón González-García¹, Juan Heriberto Torres-Jasso³ and Josefina Yoaly Sánchez-López¹

¹Division of Genetics, Biomedical Research Center of the West, Instituto Mexicano del Seguro Social; ²Human Genetics Doctorate Program, University Center of Health Sciences, Universidad de Guadalajara, Guadalajara, Jal.; ³Department of Biological Sciences, Division of Biological Sciences and Health, University Center of the Coast, Universidad de Guadalajara, Delegación Ixtapa, Puerto Vallarta, Jal. Mexico

Abstract

Gastric cancer (GC) is the third leading cause of cancer death worldwide; both environmental and genetic factors are involved in the etiology of this neoplasia. The human epidermal receptor (HER) pathway is essential for proliferation and differentiation of normal cells; but it is also implicated in the growth of cancer cells. In this work we investigate the molecular alterations in genes that encodes for HER receptors reported in GC, as well the role as therapeutic targets. We reviewed the literature reported to date regarding overexpression of HER-receptors, amplification and somatic mutations in ERBB genes occurred in gastric tumors, as well as the anti-HER therapies tested for treatment of GC. In GC, the overexpression of HER family is reported in a range of 12–87% of cases; up to 67% of cases with amplification, and 90 somatic mutations in ERBB genes. The only drug anti-HER approved for using combined with chemotherapy, in treatment of patients with advanced GC is trastuzumab; however, other targeted therapies are being investigated. The role of the HER family as a therapeutic target has not shown significant improvements in recent years; hence, further studies are required to find better options for treatment of GC.

KEY WORDS: Cell proliferation. Gene amplification. ERBB genes. Signal transduction. Stomach neoplasms.

Introduction

Globally, gastric cancer (GC) is the fifth most common type of cancer and the third cause of cancer-related death¹. Several cancer-related signaling pathways are activated in GC. The human epidermal receptor (HER) pathway is one of the most important signal-transduction pathways implicated in tumor growth and differentiation in different types of cancer, including GC².

The HER family is a group of four tyrosine kinase transmembrane proteins: HER1 (EGFR or ERBB1), HER2 (NEU or p185^{HER2}), HER3 and HER4. The HER family plays an important role in cell proliferation, differentiation and migration in normal cells, as well as

in invasion, angiogenesis, metastasis and apoptosis in tumor cells³ (Fig. 1).

Three pathways are recognized in HER signaling: phosphatidylinositol 3-kinase (PI3K)/AKT (PKB), RAS/RAF/MEK/ERK1/2 and phospholipase C (PLCg)^{3,4}. The PI3K/AKT pathway plays an important role in cell survival mediation, whereas RAS/ERK1/2 and the PLCg pathways participate in cell proliferation.

Molecular alterations in the HER family

Overexpression

Immunoreactivity for HER overexpression is categorized as 0 (< 10% of cells with weak membrane

Correspondence:

Josefina Yoaly Sánchez-López
Sierra Mojada, 800
Col. Independencia
C.P. 44340, Guadalajara, Jal., México
E-mail: yosalo1795@yahoo.com

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Figure 1. General diagram of the dimerization process and the main signaling pathways of the HER receptor family. Binding to the ligand affects the I and III domains (except for HER2).

reactivity), 1+ (> 10% of cells with partial and weak membrane activity), 2+ (> 10% of tumor cells with mild to moderate activity at the basolateral or complete membrane). Gastric tumors with an IHC 3+ classification are considered to be HER-positive (overexpression); in contrast, samples with IHC 2+ must be evaluated with in situ hybridization in order to establish the HER expression status⁵.

HER1 overexpression in gastric tumors broadly varies (2-63% of cases)⁶⁻⁸. HER1 overexpression is mainly localized in the cytoplasm (45% of cases), while

only in 9% it exhibits membrane expression⁷⁻⁹ and is not found in the nucleus. Overexpression has been associated with old age, a more aggressive course of the disease (poor differentiation, diffuse type and infiltrating capacity), proximal localization and advanced stage of disease⁶; however the prognostic role of HER1 overexpression in GC is not clear since, in some studies, HER 1 positivity was significantly associated with poor prognosis^{10,11}, whereas other authors failed to demonstrate a significant correlation between these factors^{7,12,13}.

HER2 overexpression also broadly varies in GC (from 4.4 to 53.4% of cases)¹⁴. Overexpression is more common in the cytoplasm (62%) than in the membrane (17%), and is also more common in the intestinal (32%) than in the diffuse subtype (21%)^{6,14}, as well as in older patients⁷.

HER3 is overexpressed in 87% of gastric tumors¹⁵, and is more common in the cytoplasm (64%) than in the nucleus (34%) or the membrane (2%)^{6,7}, although Choi et al.¹⁵ observed that HER3 is mainly found in the nucleus. For some authors, HER3 overexpression is associated with intestinal subtype GC^{6,7,16}, while for others, it is related to the diffuse subtype¹⁷. On the other hand, a lack of association with any GC subtype has also been described^{18,19}. In addition, overexpression is associated with well- and moderately-differentiated tumors, older age, greater tumor invasion, lymph node involvement, tumor metastasis and poor survival rate^{6,7,18}. HER3 nuclear expression in GC is associated with vascular and lymphatic invasion, as well as with poor survival (HER3+ 24-38 months vs. HER3- 45-47 months)^{6,16}.

HER4 expression appears to be higher in gastric tumor tissues than in adjacent gastric mucosa⁶. Overexpression is cytoplasmic in 23-24% of cases, membranous in 15-18% and nuclear in 2%^{6,7}. HER4 overexpression is associated with tumor characteristics of good prognosis, such as intestinal subtype, good or moderate differentiation and no vascular, lymphatic or perineural invasion⁶. This is consistent with the role of HER4 in differentiation and antiproliferative response²⁰. In spite of its alleged implication in a better prognosis in patients with GC, some reports have demonstrated that HER4 overexpression is associated with advanced stages of the disease¹⁶ and with the presence of signet-ring cells²¹.

Amplification

ERBB genes amplification is defined as positive when the HER: CEP signals ratio is ≥ 2 . Chromosome polysomy is defined as ≥ 3 CEP signals on average per cell. In the fluorescent or chromogenic in situ hybridization-based analysis, a dual coloration system is used, with the probe for any of the *EGFR*, *ERBB2*, *ERBB3* or *ERBB4* and with the respective chromosome-specific centromeric probe (CEP). *EGFR* gene amplification has been identified in 2-29%²²⁻²⁵ of GC cases, and chromosome 7 polysomy, in 3-10% of cases. *ERBB2* amplification is reported in 8 to 22.1% of gastric tumors^{5,6,22,26-30}, and is associated with the

intestinal subtype, with well- or moderately-differentiated gastric tumors, and with reduced survival (17 months for HER2+ vs 40 months for HER2-)⁶. *ERBB3* amplification has not yet been observed in GC⁶. *ERBB4* in GC was reported by Nielsen et al.²⁰ in 67% of cases, but Begnami et al.⁶ did not observe *ERBB4* gene amplification, which denotes the heterogeneity between gastric tumors.

Mutations in genes that encode the HER family

The analysis of mutations in the HER family genes has been carried out more frequently in the tyrosine kinase domain than in other domains^{23,31-37}. Mutations have not been detected in all studies, in part due to the analyzed tumor (diffuse or intestinal), tumor status, and even due to ethnic differences^{33,34,38-42}.

In GC, at least 90 somatic non-synonym mutations have been reported in *ERBB* genes, out of which 86 are missense, three are nonsense mutations and one is the deletion of an entire codon (Table 1).

The distribution of these mutations in each *ERBB* gene is: 19 in *EGFR*, 34 in *ERBB2*, 20 in *ERBB3* and 17 in *ERBB4*. These mutations affect all domains of the receptor, although more frequently the tyrosine kinase domain (27/90, 30.0%) (Fig. 2). Holbrook et al.⁴³ identified 50% (44/88) of these mutations and determined their possible functional impact; furthermore, they predicted that 28 of them can have an important role in the development or progression of cancer (Table 1).

Mutations in the EGFR gene

Mutations in the *EGFR* gene in GC are rare or absent, according to most reports. Their incidence varies in different studies from 0%^{33,38-41}, to 5.1%^{31,32} and up to 30%⁴³. Nineteen different somatic mutations have been observed (17 missense and two nonsense), mainly occurring in the tyrosine kinase domain (7/19) and domain II (5/19) (Fig. 2 and Table 1). Some recurrent somatic mutations were observed in two or more cases of GC: V308A, V505G and Y1016S. Moutinho et al.²³ carried out an analysis of the correlation between alterations in the *EGFR* gene and clinical characteristics, and suggested that *EGFR* is implicated in tumor size and progression regulation. Activating mutations in *EGFR* are not frequent in GC, but other alterations, such as mutations or copy number variations, are implicated in an

Table 1. Somatic mutations in *ERBB* family genes reported in gastric cancer

<i>EGFR</i> (n = 19)	<i>HER2</i> (n = 34)	<i>HER3</i> (n = 20)	<i>HER4</i> (n = 17)
^c K189T ⁴²	^{e,i} I101V ⁴³	^d D769H ³⁴	^{f,j} V104M ⁴⁴
^c W200X ⁴²	^e T216P ⁴³	^d G776S ³⁵	^{h,i} L91P ⁴³
^a C232S ⁴³	^e D234A ⁴³	^d V777L ³⁴	^{h,j} V226I ⁴³
^a V308A ⁴³	^e C235S ⁴³	^d Q799P ³⁴	^h K324N ⁴³
^a R309G ⁴³	^{e,i} D277Y ⁴³	^d V842I ³³	^{h,j} I329M ⁴³
^a C311G ⁴³	^e V296L ⁴³	^d T862A ⁴²	^{h,i} A380E ⁴³
^a V505G ⁴³	^{e,i} V308G ⁴³	^d L869Q ³⁴	^{h,i} H505P ⁴³
^c T638M ⁴²	^d S310F ⁴²	^e E914G ⁴³	^h W513G ⁴³
^b C646X ⁴³	^e C331G ⁴³	^e L994W ⁴³	^h A773S ³⁷
^b N647D ⁴³	^e D417H ⁴³	^{e,i} G995A ⁴³	^h L798R ⁴²
^c A767V ²³	^e D417A ⁴³	^{e,i} Q1206H ⁴³	^{h,i} K966T ⁴³
^c C781S ³²	^{e,i} T526P ⁴³	^e A1216D ⁴³	^h F974V ⁴³
^c Y801C ³¹	^{e,i} N530T ⁴³	^e F1217S ⁴³	^h F1064L ⁴²
^c N842D ²³	^{e,i} L637V ⁴³	^e F1217C ⁴³	^h E1199K ⁴²
^c V843I ⁴²	^e C642S ⁴³	^{f,j} Q809R ⁴⁴	^h E1201X ⁴³
^c L858R ³¹	^d R678Q ⁴²	^f K926R ⁴³	^h A1233G ⁴²
^c G863D ²³	^d K724N ³⁴	^f E928G ³⁶	^h R1250Q ⁴²
^c Y1016S ⁴³	^d T733I ³⁴	^f L930W ⁴³	
^{c,i} V1109D ⁴³	^d I740T ⁴²	^f R1089W ⁴⁴	
	^{d,e} L755S ^{34,43}	^f I218delE ³⁶	

Number of sequences used to name each mutation: ^aHM_201282 (628 aa); ^bNM_201284 (705 aa); ^cNM_0055228 (1210 aa); ^dNM_004448 (1255 aa); ^emutations described by Holbrook et al.⁴³ considering the 1225 aa (NM_001005862) isoform were named by us according to isoform 1255 aa (NM_004448); ^fNM_001982 (1342 aa); ^gNM_001005915 (183 aa); ^hNM_005235 (1308 aa); ⁱmutations with a SIFT score > 0.05: the amino acid change possibly does not significantly affect the protein function; ^jevidence of wild-type HER2 oncogenic activity.

increase of diffuse tumors size; in addition, alterations in this gene have been suggested to confer an invasive behavior in neoplastic cells.

***ERBB2* gene mutations**

Only few studies have been conducted to identify *ERBB2* somatic mutations in GC in comparison with lung and breast cancers. *ERBB2* mutation rate in GC ranges from 2%³³⁻³⁵ to 60%⁴³; however, of the 30 mutations detected by Holbrook et al.⁴³, 14 seem to be of little importance for the development or progression of cancer, thus decreasing the frequency of *ERBB2* mutations with tumoral impact to 32%. So far, 34 *ERBB2* different missense variants have been described, out of which 13 were detected in the tyrosine kinase domain^{33-35,42,43} (Fig. 2) and in advanced GC³⁴. Similarly as observed for *EGFR*, most mutations in *ERBB2* are heterogeneous in different types of

tumors. Very few mutations are recurrent, such as D204A, L755S, R678Q and V777L, among others^{34,42,43}. Some mutations are observed in several patients with the same type of cancer and other in patients with different types of cancer. On the other hand, the same codon is changed by different amino acids, suggesting the presence of hot spots; for example, L755S/W/P, D769H/Y, G776S/L/V and V777L/M^{34,35,45-47}. The L755S mutation (called L725S by Holbrook et al.⁴³) is one of the most frequently observed mutations in several types of cancer. The somatic mutations D769H, D769Y, V777L and V842I are activating mutations that can promote cell proliferation by themselves⁴⁵.

***ERBB3* gene mutations**

The frequency of mutations in the *ERBB3* gene in GC ranges from 0.6%⁴⁸ to 13%⁴⁴. Currently, at least 20

Figure 2. Localization of mutations reported to affect the *ERBB3*-HER receptor family in gastric cancer. Mutations marked with an asterisk were described by Holbrook et al.⁴³ considering the 1225 amino acid (NM_001005862) isoform; we relocated them according to the 1255 amino acid (NM_004448) isoform.

somatic mutations in *ERBB3* have already been identified (19 missense and one complete codon deletion). Unlike observations for *EGFR* and *ERBB2*, most mutations occur within domain III, which participates in the ligand binding^{36,42,43,44} (Fig. 2). Jaiswal et al.⁴⁴ analyzed the functional impact of four *ERBB3* gene mutations (V104M, A232V, P262V, P262H and Q809R) and

found evidence of oncogenic potential in all of them. On the other hand, Holbrook et al.⁴³ analyzed five mutations of the *ERBB3* gene (A172P, D297Y, V654G, K926R and L930W) and found a possible clinical relevance for GC. Most these mutations have functional importance, as they affect interactions that are necessary for dimerization or ligand binding⁴⁴.

Mutations in the *ERBB4* gene

The frequency of *ERBB4* mutations in GC ranges from 0.6%³⁷ to 28%⁴³. There are at least 17 different somatic mutations reported in GC (16 are missense and one nonsense). Mutations are distributed across the entire gene; however, a slight accumulation is observed at the C-terminal domain (Fig. 2 and Table 1). Although no functional characterization of *ERBB4* gene mutations has been made in GC, Holbrook et al.⁴³ calculated the potential of 10 variants and found that at least 4 mutations (K324N, W513G, F974V and E1201X) can be clinically important for the development of cancer.

Targeted therapies against the HER receptor family

There are two classes of anti-HER therapy: monoclonal antibodies and small molecule tyrosine kinase inhibitors. Anti-HER monotherapy for GC is less toxic, but also less efficient, and combination of agents targeted against HER with traditional chemotherapeutic agents is therefore most commonly used.

Monoclonal antibodies

Anti-HER1 therapies

Cetuximab is a chimeric monoclonal antibody-type G1 immunoglobulin (IgG1) that binds to HER1 extracellular domain and competitively inhibits the binding to EGF ligand and other ligands, as well as ligand-induced tyrosine kinase phosphorylation. Cetuximab also induces *EGFR* internalization, downregulation and degradation⁴⁹. It was the first anti-EGFR antibody approved by the US Food and Drug Administration (FDA) for the treatment of squamous cell carcinoma and advanced wild-type KRAS colorectal cancer^{50,51}. It is the most widely investigated anti-HER1 therapy in GC⁵²⁻⁵⁴. It hasn't had a significant impact on survival (3.1-16.6 months) or on progression-free survival (1.6-11 months) in patients with GC and gastroesophageal cancer (GEC) (Table 2); nevertheless, there is the registry of one patient with metastatic GC treated with cetuximab with the longest progression-free survival reported (7 years and 11 months)⁸².

Panitumumab is the first completely human IgG2 monoclonal antibody approved for the treatment of *EGFR*-expressing metastatic colorectal cancer,

based on results that showed clinical benefits⁸³. One phase III trial (REAL-3) assessed panitumumab in treatment-naïve patients with advanced esophageal cancer and GC, but the results showed no survival increase⁶⁸ (Table 2). Other four clinical trials were discontinued owing to a lack of efficacy of panitumumab added to chemotherapy⁸⁴. The failure of randomized phase III trials using cetuximab or panitumumab in combination with chemotherapy was due to the lack of selection of a specific patient population according to *EGFR* expression and to the negative interaction of the anti-EGFR monoclonal antibody and the therapeutic agent. More recent studies are assessing panitumumab efficacy in combination with other components⁸⁴.

Matuzumab is a humanized IgG1 monoclonal antibody against HER1. In a randomized phase II trial conducted in patients with advanced GC with HER1 overexpression, matuzumab + epirubicin + cisplatin + capecitabine were evaluated as first-line therapy, and the results showed that the combination of matuzumab with chemotherapy does not improve survival rates (Table 2); therefore, matuzumab was not tested in phase III trials^{69,85}.

Nimotuzumab is a humanized IgG1 that has demonstrated efficacy without serious skin toxicity as the one caused by other HER1-binding therapies; however, survival is similar to that observed with other drugs⁷⁰⁻⁷² (Table 2).

Anti-HER2 therapies

Trastuzumab is a humanized monoclonal antibody that binds to HER2 extracellular domain IV and prevents intracellular tyrosine kinase activation. It was approved for use in combination with chemotherapy as an adjuvant for patients with HER2+ breast cancer and for advanced GC therapy in HER2+ treatment naïve patients in combination with chemotherapy. However, trastuzumab confers higher risk of cardiotoxicity⁸⁶, which is partially reversible after the antibody is eliminated^{53,87}. The only study that has demonstrated strong evidence for survival improvement was the phase III ToGA trial, which included patients with HER2+ GC (Table 2); patients with IHC 2+ tumors and positive fluorescent in situ hybridization or IHC 3+ tumors had a marked survival improvement (16.0 months)³⁰.

Pertuzumab is a humanized monoclonal antibody that binds to the HER2 dimerization domain II, unlike trastuzumab, which binds to domain IV. It inhibits

Table 2. HER-targeted therapies for patients with gastric cancer (studies with published results)

Drug	Target	Combined with chemotherapy	PFS (months)	MS (months)	Reference
Monoclonal antibodies					
Cetuximab HER1		Irinotecan, leucovorin, 5FU [†]	8–9	16–16.6	Pinto, et al. ⁵⁵
					Kanzleer, et al. ⁵⁶
					Moehler, et al. ⁵⁷
		Cisplatin, leucovorin, 5FU [†]	11	14.5	Yeh, et al. ⁵⁸
		Oxaliplatin, capecitabine [†]	6.5	11.8	Kim, et al. ⁵²
		Oxaliplatin, leucovorin, 5FU [†]	5.5	9.9	Han, et al. ⁵⁹
		Oxaliplatin, docetaxel [†]	5.1	9.4	Richards, et al. ⁶⁰
		Cisplatin, docetaxel [†]	5	9	Pinto, et al. ⁶¹
		Capecitabine, cisplatin [†]	4.4	9.4	Lordick, et al. ⁶²
		Irinotecan, leucovorin, 5FU [†]	4.9	8.1	Li, et al. ⁶³
		Irinotecan [†]	2.8	6.1	Schonnemann, et al. ⁶⁴
		Irinotecan [†]	1.7	3.2	Park, et al. ⁶⁵
		Irinotecan, leucovorin, 5FU [†]			
		Irinotecan, cisplatin [†]			
		Oxaliplatin, leucovorin, 5FU [†]			
		Docetaxel, cisplatin [†]			
		Docetaxel [†]	2.1	5.4	Tebbutt, et al. ⁶⁶
		None [‡]	1.6	3.1	Chan, et al. ⁶⁷
Panitumumab	HER1	Epirubicin, oxaliplatin, capecitabine [†]	6	8.8	Waddell, et al. ⁶⁸
Matuzumab	HER1	Epirubicin, cisplatin, capecitabine [†]	4.8	9.4	Rao, et al. ⁶⁹
Nimotuzumab	HER1	Cisplatin, S-1 [†]	5	–	Wang, et al. ⁷⁰
		Irinotecan [†]	2.4	8.3	Satoh, et al. ⁷¹
		Docetaxel, cisplatin, 5FU [†]	6.5	12.5	Xu, et al. ⁷²
Trastuzumab HER2		5FU, capecitabine, cisplatin [†]	6.7	13.8	Bang, et al. ²⁹
Tyrosine kinase inhibitors					
Erlotinib	HER1	Alone [†]	GC 1.6	3.5	Dragovich, et al. ⁷³
			GEC 3	6.7	
		Oxaliplatin, leucovorin, 5FU [†]	5.5	11	Wainberg, et al. ⁷⁴
Gefitinib	HER1	Alone [†]	-	5.5	Aldestein, et al. ⁷⁵
		Cisplatin, 5FU, radiotherapy [†]	-	24.2	Rodriguez, et al. ⁷⁶
Lapatinib	HER1	Alone [†]	2	4.8	Iqbal, et al. ⁷⁷
		Capecitabine [†]	1.6	–	Lorenzen, et al. ⁷⁸
		Capecitabine, oxaliplatin [†]	6	12.2	Hecht, et al. ⁷⁹
		Paclitaxel [†]	5.4	11	Satoh, et al. ⁸⁰
Dacomitinib	HER1,2,4	Alone [†]	2.1	7.1	Lee, et al. ⁸¹

MS: mean survival; PFS: progression-free survival. †: first line treatment; ‡: second line treatment.

HER2 dimerization with other HER family members and exhibits antibody-dependent cell cytotoxicity (ADCC)-related anti-tumor activity^{88,89}. The effect of adding pertuzumab to chemotherapy is currently being investigated⁸⁴.

One meta-analysis suggested that anti-HER1 monoclonal antibodies-based therapies result in lower survival rates than anti-HER2 therapies. However, chemotherapy together with anti-HER2 targeted therapy significantly increases the risk of diarrhea, hypocalcemia, mucositis and rash in comparison with chemotherapy alone⁸⁵.

Trastuzumab emtansine (T-DM1) is an antibody that combines trastuzumab and a maitansine-derived microtubule inhibitor (DM1). This drug combines two strategies: trastuzumab anti-HER2 activity and targeted intracellular DM1 delivery, which interferes with mitosis and promotes apoptosis. Its use in HER2+ breast cancer has already been approved⁹⁰. Clinical trials are recruiting patients in order to assess T-DM1 together with chemotherapy in patients with GC^{84,88,91}.

Therapies against HER2-HER3 heterodimers

MM-111 is a bispecific fusion antibody that comprises anti-HER2 and anti-HER3 antibodies bound by human serum albumin. MM-111 binds to HER2 and HER3-expressing cells and blocks ligand-induced signaling⁹².

Tyrosine kinase inhibitors

HER1 inhibitors

Erlotinib has been approved for the treatment of lung and pancreatic cancer⁵⁴. In a phase II trial, erlotinib was found to be active in patients with gastroesophageal cancer, but good response was not obtained in patients with GC⁷³ (Table 2). In a phase II trial, a combination of erlotinib, oxaliplatin, leucovorin and 5-fluorouracil (5FU) was administered to treatment-naïve patients with advanced or metastatic esophageal cancer and gastroesophageal cancer; the results were similar to those previously reported⁷⁴ (Table 2).

Gefitinib was approved by the FDA for the treatment of advanced non-small cell lung cancer⁵⁴. As monotherapy, it is associated to low survival⁷⁵, but in combination with cisplatin, 5FU and radiotherapy, it has shown the

highest survival rate (24.2 months) in esophageal and gastroesophageal cancer⁷⁶ (Table 2).

Neratinib acts by covalently binding to a cysteine lateral chain in the HER receptor. It is directed to patients with activating mutations in the *EGFR*, *ERBB2* or *ERBB3* genes and to patients with *EGFR* amplification.

HER1/HER2 inhibitors

Lapatinib is an orally-active molecule for HER1 and HER2 double-inhibition that has been approved to be used in HER2+ breast cancer. It is an inhibitor more potent for HER1 and HER2 than for HER4 (> 10x)⁹¹. It obtained the best results in patients with advanced GC with paclitaxel⁷¹ and in combination with capecitabine and oxaliplatin⁷⁹, in comparison with single-agent administration⁷⁷ or in combination only with capecitabine⁷⁹ (Table 2).

Afatinib is an irreversible HER1 and HER2 inhibitor that has demonstrated anti-tumor activity in vivo in patients with HER2+ GC^{91,93}. Clinical trials are assessing its efficacy in combination with trastuzumab and with cisplatin plus 5FU⁸⁴.

Pan-inhibitors (HER1/HER2/HER4)

AST1306 is an orally active, highly selective and irreversible HER inhibitor with promising anticancer activity in patients with previously-treated, advanced solid tumors. Partial response was confirmed in 12.7% of patients (among them, one with GC), and stable disease for ≥ 6 months was observed in 12.7% of patients. AST1306 can potentially inhibit the EGFR T790M mutation, which is commonly associated with acquired resistance to first-generation HER1 inhibitors in non-small cell lung cancer⁹⁴.

Dacomitinib induces apoptosis and arrests the cell cycle in G1, and also inhibits signaling pathways phosphorylation and transduction in HER2+ GC cells. In addition, it blocks the formation of HER1/HER2, HER2/HER3 and HER3/HER4 heterodimers. Synergy has been observed with many commonly employed cytotoxic agents (5FU, cisplatin, docetaxel and paclitaxel) and with targeted agents, such as trastuzumab⁹⁵. Dacomitinib was used in patients with HER2+ advanced GC as single agent after failure of at least one previous chemotherapy regimen, but no substantial survival improvement was observed⁸¹ (Table 2).

Pozotinib inhibits the phosphorylation of the HER family members and molecules of the signaling cascade. It also induces apoptosis and cell cycle arrest at phase G1. Although this agent was inactive as monotherapy in HER2- cell lines, synergy was reported in both HER2+ and HER- models⁹⁶.

AZD8931 provides EGFR, HER2 and HER3-signaling inhibition. The efficacy of this drug in combination with paclitaxel was assessed in patients with advanced GC; however, the trial was prematurely stopped due to the low response observed⁸⁴.

Conclusions

The conducted review allows observing that there is broad heterogeneity in molecular alterations such as overexpression and amplification in GC; somatic mutations are not common since, worldwide, only 88 different mutations have been reported in the four genes that encode the HER proteins.

Meanwhile, the treatments focused on improving the quality of life and prolonging survival in patients with advanced GC have not shown significant improvements in the past few years; therefore, further studies are required in order to identify the best options for the treatment of these patients. The fact that ethnic differences have been observed in the survival results in patients with other malignancies in response to the treatment with tyrosine kinase inhibitors and chemotherapy (which also were observed in cases of GC) is of great importance, and it should therefore be taken into account. Fortunately, a larger number of studies are currently considering the patients' molecular profile in the search for treatments, which may generate a better response to the drugs.

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