

HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target

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Gastric cancer is the second leading cause of cancer mortality in the world and its management, especially in advanced stages, has evolved relatively little. In particular, no targeted modality has so far been incorporated to its treatment armamentarium. HER2 overexpression is increasingly recognized as a frequent molecular abnormality, driven as in breast cancer by gene amplification. There is mounting evidence of the role of HER2 overexpression in patients with gastric cancer, and it has been solidly correlated to poor outcomes and a more aggressive disease. Additionally, preclinical data are showing significant antitumor efficacy of anti-HER2 therapies (particularly monoclonal antibodies directed towards the protein) in *in vitro* and *in vivo* models of gastric cancer. As a result, several clinical trials are exploring in different settings and with diverse designs the potential of anti-HER2 therapies in gastric cancer patients. This review summarizes the rationale, preclinical evidence, retrospective clinical analyses, and the interim clinical data pertaining HER2 therapies in gastric cancer.

Key words: c-ErbB-2, gastric cancer, gastroesophageal adenocarcinoma, HER2, prognostic factor, trastuzumab

Introduction

Gastric cancer is one of the most common tumors and remains the second leading cause of cancer mortality in the world [1]. Barrett's esophagus and dysplasia are associated with the development of esophageal adenocarcinoma [2] while helicobacter pylori infection, atrophic gastritis, intestinal metaplasia, and dysplasia are related with gastric adenocarcinoma [3].

Surgical resection is the mainstay of treatment and can cure patients with early-stage cancer. The survival rate of patients with advanced resectable gastric or gastroesophageal junction (GEJ) cancers, however, remains poor despite new treatment strategies, such as perioperative chemotherapy [4] or adjuvant chemoradiation [5].

In Western countries, most gastric cancer patients are diagnosed when the tumor is at an unresectable stage. For these patients, systemic chemotherapy is the main treatment option because it prolongs survival without quality of life compromise. Many single agents and combinations are active in the treatment of metastatic disease. Objective response rates range from 10% to 30% for single-agent therapy and 30% to 60% for combination regimens [6]. Platinum compounds, fluoropyrimidines, antracyclines, and, recently, taxanes and

irinotecan are the most active drugs. Although a large number of chemotherapy regimens have been tested in randomized studies, there is no internationally accepted standard of care, and uncertainty remains regarding the choice of the chemotherapy regimen [7].

Survival of patients with advanced gastric cancer treated with palliative chemotherapy remains low. New therapies are urgently needed. A better understanding of the molecular basis of cancer has contributed to the development of rationally designed molecular targeted therapies, which interfere with the signalling cascades involved in cell differentiation, proliferation, and survival. The HER2 protein (p185, HER2/neu, ErbB-2) is a 185-kDa transmembrane tyrosine kinase (TK) receptor and a member of the epidermal growth factor receptors (EGFRs) family. This family is composed of four members: HER1 (also known as the EGFR), HER2, HER3 (also termed ErbB-3), and HER4 (also termed ErbB-4). These receptors share the same molecular structure with an extracellular ligand-binding domain, a short transmembrane domain, and an intracellular domain with TK activity (excepting the HER3). The binding of different ligands to the extracellular domain initiates a signal transduction cascade that can influence many aspects of tumor cell biology, including cell proliferation, apoptosis, adhesion, migration, and differentiation. Ligand binding induces EGFR homodimerization as well as heterodimerization with other types of HER proteins. HER2 does not bind to any known ligand, but it is the preferred heterodimerization partner for other members of the HER family. HER2 is encoded by a gene

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located on chromosome 17q21 [8, 9]. The *HER2* gene, located adjacent to the topoisomerase IIa genes, is related to the oncogene *v-erbB* of the avian erythroblastosis virus. In carcinomas, *HER2* acts as an oncogene, mainly because high-level amplification of the gene induces protein overexpression in the cellular membrane and subsequent acquisition of advantageous properties for a malignant cell [10].

Recent studies indicate a role of HER2 in the development of numerous types of human cancer. HER2 overexpression and/or amplification have been detected in 10%–34% of invasive breast cancers and correlate with the clinical outcome, confer poor prognosis, and also constitute a predictive factor of poor response to chemotherapy and endocrine therapy [11]. HER2 overexpression and/or amplification have also been observed in colon [12], bladder [13], ovarian [14], endometrial [15], lung [16], uterine cervix [17], head and neck [18], esophageal [19], and gastric carcinomas.

Trastuzumab (Herceptin™) is a monoclonal antibody which specifically targets HER2 protein by directly binding the extracellular domain of the receptor. Trastuzumab enhances survival rates in both primary and metastatic HER2-positive breast cancer patients [20, 21]. The efficacy of trastuzumab in breast cancer patients has led to investigate its antitumor activity in patients with HER2-positive cancers, including gastric adenocarcinomas.

The aim of this article is to review the role of HER2 as a prognostic factor and the efficacy and tolerance of trastuzumab-based therapy in patients with advanced nonresectable HER2-positive gastric or GEJ adenocarcinomas.

HER2 expression as a prognostic factor in gastric cancer

The TNM stage is the most important prognostic factor for gastric cancer. This classification system establishes the stage depending on the depth of invasion of gastric wall (T), the involvement of lymph nodes (N) and the presence of distant metastasis (M). Prognosis, however, varies among patients in the same stage. Therefore, additional classification parameters need to be defined in addition to the TNM and the classic pathologic characteristics of the tumor in order to better identify the biologic subsets of this disease.

Biological prognostic factors are often derived from the genetic process, which is thought to represent a crucial step to

gastric cancer (HER2, E-cadherin, EGFR, DNA copy number changes, microsatellite instability, and changes in expression of several factors including thymidilate synthase, beta-catenin, mucin antigen, p53, COX-2, matrix metalloproteinases, and vascular endothelial growth factor receptor) [22]. Some of these potential prognostic factors can also be predictive of response to therapy as they are a molecular target either to chemotherapeutics or to biologic/targeted therapies [22], such as trastuzumab in HER2-positive tumors.

Overexpression of HER2 protein in gastric cancer, using immunohistochemistry (IHC), was first described in 1986 [23]. In 1990s, some series reported a 9%–38% of HER2-positive tumors using polyclonal antibodies directed against different domains of HER2 protein and restricting the evaluation to the staining of the cell membrane [24–26]. More recent studies, which determined HER2 overexpression by IHC using monoclonal antibody (HercepTest) and/or gene amplification by FISH, have observed similar rates (Table 1). In a Japanese series, HER2 overexpression by IHC was found in 23% and gene amplification by FISH in 27% of 200 resected tumors [27]. Our group reported a 13% of positive HER2 expression (IHC = 2+/FISH+ or IHC = 3+) in a series of 166 biopsy or surgical specimens of gastric cancer patients [28]. We also observed that positive HER2 expression varied depending on the histology (intestinal type 16%, diffuse type 7%, unknown 14%; $P = 0.276$) and the primary tumor localization [25% GEJ versus (vs) 9.5% gastric; $P = 0.01$]. Following a modified HER2 scoring system, Lordick et al. [31] are centrally testing tumor samples using both IHC and FISH to identify eligible patients for enrollment in the ToGA clinical trial, which is discussed later. In their abstract presented at European Cancer Organization 2007, 341 (22%) of 1527 tumors were HER2 positive. HER2 positivity differed significantly by histological subtype (intestinal 34%, diffuse 6%, mixed 20%) and according to the site of the tumor (32% GEJ and 18% gastric localization). An update of this study, recently presented at 2008 Gastrointestinal Cancers Symposium, described an overall HER2 expression (IHC 3+ and/or FISH +) of 22% in 2168 patients tested and confirmed a higher rate of HER2 positivity in GEJ tumors than in gastric cancer samples (34% vs 20%) [32].

The role of HER2 as a prognostic factor in gastric cancer has been controversial because some of the initial studies failed to find an association with prognosis [33, 34]. Other authors, however, reported a direct correlation between HER2

Table 1. HER2 expression in gastric or gastroesophageal junction cancer

Author	n	Geographic zone	Overexpression (%)	IHC	Amplification	Method
Yano et al. [27]	200	Japan	23	HercepTest	27%	FISH
Gravalos et al. [28]	166	Europe	13 ^a	HercepTest	If IHC 2+	FISH
Allgayer et al. [29]	203	Europe	91	MoAc + streptavidin–biotin–elite kit	–	–
Park et al. [30]	182	Korea	16	HercepTest	Seven patients	FISH/CISH
Lordick et al. [31]	1527	Europe, Asia, Latin America	22 ^a	HercepTest	–	FISH

^aHER2 expression using IHC and/or FISH.

IHC, immunohistochemistry; CISH, chromogenic in situ hybridization.

expression and poorer survival. In a series of 260 gastric cancers, HER2 expression was an independent factor and HER2 staining intensity was correlated with tumor size, serosal invasion, and lymph node metastases [24]. In a retrospective study of 108 cases, HER2 overexpression was associated with a poorer 10-year survival [35]. In another study, a significantly poorer prognosis was observed in HER2-positive early gastric cancer in a series of 226 patients [36]. Finally, Nakajima et al. [37] considered that in early-stage tumors, HER2 overexpression is the second poorest prognostic variable after nodal status.

Between 2000 and 2007, some new relevant studies have been reported. Allgayer et al. [29] found a very high rate of membranous or cytoplasmatic HER2 expression using IHC in a prospective series of 203 gastric cancer patients. Two major explanations for this considerable discrepancy in HER2 expression between previous studies (up to 38% positive cases) and their series (91% positive cases) are the following: first, in contrast to the previous studies in gastric cancer, they used a monoclonal antibody against HER2 together with a highly sensitive streptavidin–biotin–elite kit and, second, the previous studies restricted their evaluation to membrane staining, excluding staining that appeared cytoplasmatic. A significant association of increasing expression of HER2 on IHC with shorter disease-free survival and overall survival (OS) was observed. In addition to surgical curability, pT stage, pN stage, and plasminogen activator inhibitor, HER2 was an independent prognostic factor for OS of curatively resected patients [($P = 0.049$; relative risk (RR) = 1.54; 95% confidence interval (CI) = 1.08–1.67] and for survival of all patients ($P = 0.028$; RR = 1.33; 95% CI = 1.28–1.38). Spanish investigators also reported HER2 expression as a factor for poor prognosis [38].

Tanner et al. [39] observed HER2 amplification by chromogenic *in situ* hybridization (CISH) in 12% of 131 gastric adenocarcinomas and in 24% of 100 GEJ tumors. HER2 amplification was strongly associated with the intestinal histologic type according to Lauren's classification (intestinal type 21.5%, diffuse type 2%, mixed/anaplastic type 5%; $P = 0.005$), but it was not associated with gender, age at diagnosis, or clinical stage in any of the tumor groups studied. Presence of HER2 amplification was significantly associated with poor carcinoma-specific survival ($P = 0.0089$); median survival of patients with HER2-negative cancer (12.7 months) was twice as long as that of patients with cancer with HER2 amplification (6.6 months), although the difference was not statistically significant ($P = 0.37$). This prevalence of *HER2* gene amplification (12%) in gastric adenocarcinomas was within the same range as found in a FISH-based study recently reported by

Takehana et al. [40], who found HER2 to be amplified in ~8% of the cases.

Finally, in a Korean study, HER2 overexpression and gene amplification with semiquantitative standardized IHC staining, CISH and FISH were determined in 182 gastric cancer patients who underwent curative surgery [30]. Sixteen percent expressed HER2 protein by IHC and *HER2* gene amplification was detected in seven patients by CISH and FISH. Intestinal-type cancers exhibited higher rates of HER2 amplification than did diffuse-type cancers ($P < 0.05$). Tumors with HER2 amplification were associated with poor mean survival rates (922 vs 3243 days) and 5-year survival rates (21% vs 63%; $P < 0.05$). Age, TNM stage, and amplification of HER2 were found to be independently related to survival by multivariate analysis.

HER2 expression and correlation with pathologic variables

HER2 expression and histologic type

A high correlation between HER2 expression and intestinal histologic type was reported by several authors in 1990s [41–44]. This correlation has been confirmed in more recent studies (Table 2). Our group observed a higher rate of HER2 overexpression in intestinal than in diffuse type (16% vs 7%) [28]. In the Finnish study, amplification of HER2 was strongly associated with poor carcinoma-specific survival, particularly evident in the subgroup of intestinal type of cancers ($P = 0.0019$) [40], which is usually considered to associate with more favorable prognosis than the diffuse type of gastric adenocarcinoma [45]. Intestinal-type cancers also exhibited higher rates of HER2 amplification than did diffuse-type cancers ($P < 0.05$) in the Korean study [30]. Finally, in the ToGA trial, HER2 positivity differed significantly by histological subtype (intestinal 34%, diffuse 6%, mixed 20%) [31].

The reasons for the selective overexpression of HER2 in intestinal-type gastric carcinomas are complex and it is necessary to investigate them in depth. The association of this oncogene with a specific histologic tumor type indicates that certain characteristics (e.g. HER2 overexpression and intestinal phenotype) may be expressed together preferentially. However, since not all tumors of the intestinal type overexpress HER2, this cannot be the only factor involved [30]. In breast carcinomas, *HER2* gene amplification is a common feature of invasive ductal carcinomas and an uncommon feature in lobular carcinomas. In gastric cancer, *HER2* gene amplification associates inversely with E-cadherin mutations [46]; E-cadherin

Table 2. HER2 expression and clinicohistologic characteristics

Author	n	Histologic type			P	Localization			Method
		Intestinal (%)	Diffuse (%)	Mixed/unknown (%)		GEJ (%)	Gastric (%)	P	
Tanner et al. [39]	231	21.5	2	5	0.005	24	12	–	CISH
Gravalos et al. [28]	166	16	7	14	0.27	25	9.5	0.01	IHC, FISH
Lordick et al. [31]	1527	34	6	20	–	32	18	–	IHC, FISH

GEJ, gastroesophageal junction; CISH, chromogenic *in situ* hybridization; IHC, immunohistochemistry.

mutations are typical for diffuse gastric and lobular invasive breast carcinomas, but rare in intestinal gastric and ductal invasive breast carcinomas [39]. Gene amplification and protein overexpression of the growth factor receptors HER2 and K-sam may be prognostic factors for intestinal- and diffuse-type gastric cancer, respectively [47]. Recently, germline mutations of E-cadherin have been identified that are responsible for a dominantly inherited form of diffuse-type gastric cancer [48].

HER2 expression and primary tumor site

At least three studies reported that HER2 expression is more common in GEJ cancers than in gastric tumors (Table 2). Our study showed a 25% vs 9.5% HER2 overexpression and/or amplification in GEJ and in gastric cancers, respectively ($P = 0.01$) [28]. Tanner et al. [39] also found a higher rate of HER2 positivity in GEJ cancers than in gastric tumors (24% vs 12%). These results have been confirmed in a large number of patients in the ToGA study, in which HER2 positivity was found in 32% and 18% in GEJ and gastric cancers, respectively [31].

concordance between HER2 overexpression and gene amplification

In breast cancer, it is generally thought that HER2 overexpression is principally (95%) achieved via gene amplification (increased copies of the normal *HER2* gene), thereby resulting in increased transcription of the gene, increased HER2 receptors on the cell membrane (overexpression), and increased cell proliferation [49]. For breast cancer, a standardization of the FISH and IHC assessments of HER2 amplification and overexpression has been introduced and the concordance rates between these two methods are ~73%–98% [50].

The concordance of protein expression and gene amplification of HER2 in gastric cancer, however, have been controversial. Studies published in 1990–1991 did not observe a high concordance between these two methods of assessment. In a series of 40 cases analyzed by Lemoine et al. [44], 26% were found to display elevated protein expression, but only 13% evidenced gene amplification. A similar result was also obtained by Kameda et al. [51], who detected overexpression without amplification and considered that this may indicate that gene amplification may not be the primary mechanism by which the HER2 protein is overexpressed in gastric cancer. HER2 overexpression may occur by a number of different mechanisms, including transcriptional activation by other genes or post-transcriptional events [52].

Recent studies, however, report a high concordance between overexpression in IHC and amplification by FISH or CISH. Yano et al. [27] found a concordance rate between IHC and FISH in the HER2-protein overexpression cases of 87% (58.5% for 2+ and 88% for 3+). In the ToGA trial, the concordance between HER2 positivity by IHC and FISH was 87% and differences were largely due to FISH-positive cases that were IHC 0/1+ [31].

To establish a HER2 scoring system specific for gastric cancer, Hofmann et al. [53] analyzed 178 gastric cancer samples

using IHC (HercepTest™) and FISH [pharmDX tests (Dako)]. In 2006, they reported that discrepancies between IHC and FISH occurred mainly due to basolateral membrane staining of glandular cells (resulting in incompletely stained membranes) as well as a higher percentage of heterogeneous tumors in gastric cancer in comparison with breast cancer. On the basis of these observations, they proposed modifications of the HercepTest™ score for gastric cancer samples in an international consensus meeting. This modified HER2 scoring system is being used to identify eligible patients for enrollment in the ToGA trial [31].

In gastric cancer, the concordance between surgically resected materials and the prior biopsy specimens is high [27, 31].

anti-HER2 therapy: trastuzumab

HER2 expression has become an important biomarker for identifying patients who could respond to HER2 targeting therapy using the fully humanized monoclonal antibody trastuzumab. Antitumor mechanisms proposed for the therapeutic effect of trastuzumab are two: a direct antiproliferative effect by blockade of signalling pathways, down-modulation of the HER2 protein, and activation of apoptotic signals of the tumor cells, and an indirect antitumor effect by antibody-dependent cell-mediated cytotoxicity activity [54, 55].

preclinical and murine models

Several studies indicate antitumor activity of trastuzumab in overexpressing HER2 human gastric cancer cell lines or xenograft models. Most of these experiments used the NCI-N87 and/or 4-1ST gastric cancer cell lines, which show HER2 expression in IHC and gene amplification by FISH. Tanner et al. [39] studied the sensitivity of N87 gastric cancer cell line to trastuzumab and compared its sensitivity with that of the breast cancer cell line with HER2 amplification (SKBR-3). *In vitro*, trastuzumab inhibited the growth of N87 and SKBR-3 at about equal efficacy. Growth inhibition of N87 cells when using a 5 mg/kg weekly dose of trastuzumab was also verified *in vivo* in N87 xenograft tumors.

Matsui et al. [56] used four human gastric cancer cell lines with various expression levels of HER2 protein (N87, MKN-45P, Kato-III, and MKN-1) to study the association between the expression of HER2 protein and the sensitivity to trastuzumab. Their experiment showed that trastuzumab suppressed the growth of human gastric cancer with HER2 overexpression *in vitro* and *in vivo* and improved the survival of mice with peritoneal dissemination and ascites of gastric cancer.

Finally, Fujimoto-Ouchi et al. [57] observed that HER2 protein showed potent staining in peripheral membranes in gastric cancer cell lines, similar to the staining pattern of breast cancer, and FISH scores were also comparable to those of breast cancer models. *In vitro*, trastuzumab showed direct and indirect antiproliferative activities in N87 cancer cell lines. When trastuzumab was administered to mice bearing the N87 model, significant antitumor activity was observed. In contrast,

trastuzumab administered to mice bearing HER2-negative gastric cancer xenograft, GXF97, did not show any significant antitumor activity. Trastuzumab administered in combination with chemotherapy agents for gastric cancer (paclitaxel, docetaxel, capecitabine, cisplatin, or irinotecan) showed potent antitumor activity which was significantly greater than did trastuzumab or the chemotherapeutic agents as single treatments. A three-drug combination of capecitabine, cisplatin, and trastuzumab achieved remarkable tumor growth inhibition in the N87 model. This triplet achieved a significant increase in tumor growth inhibitor as compared with trastuzumab monotherapy, trastuzumab–cisplatin, or cisplatin–capecitabine.

clinical application: clinical trials

first-line setting

In chemo-naïve patients, at least three clinical trials are exploring the addition of trastuzumab to chemotherapy in HER2-positive gastric or gastroesophageal adenocarcinoma (Table 3).

phase II of trastuzumab and cisplatin. We are conducting a phase II trial to investigate the efficacy and tolerability of trastuzumab plus cisplatin in HER2-positive advanced gastric cancer patients. Exploratory objectives include analysis of HER2 extracellular domain and correlation of the results with histological HER2 overexpression and with clinical response [58]. Main inclusion criteria are no previous chemotherapy, measurable, no operable advanced gastric or gastroesophageal adenocarcinoma, histopathologically confirmed, HER2 overexpression, and/or amplification, age ≥ 18 years, ECOG < 2 , left ventricle ejection fraction $\geq 50\%$, and adequate organ function. Prior adjuvant radiotherapy or/and chemotherapy is allowed. IHC is carried out using HercepTest™ and a FISH assay is done when IHQ = 2+. HER2 expression is positive if IHC = 2+ and FISH+ or IHC = 3+. Trastuzumab 8 mg/kg day 1 (loading dose in first cycle) and 6 mg/kg (maintenance doses) and cisplatin 75 mg/m² day 1 were administered every 21 days until progression, unacceptable toxicity, or withdrawal inform consent. Preliminary results show that 6 (35%) out of 17 assessable

patients achieved response [1/5 complete response/partial response (CR/PR)] and three (17%) stabilization [52% control disease = CR + PR + stable disease (SD)]. No grade 4 toxic effects have been documented thus far.

phase II of trastuzumab, cisplatin, and docetaxel. Cisplatin and docetaxel are active agents in the treatment of metastatic gastric cancer. Nicholas et al. [59] are conducting a multicenter single-arm phase II study to assess the activity of trastuzumab, cisplatin, and docetaxel therapy in patients with metastatic gastric or GEJ cancer either FISH+ or IHC = 3+ for HER2 overexpression. Treatment schedule consists of cisplatin 75 mg/m², docetaxel 75 mg/m², and trastuzumab [loading dose 8 mg/kg (cycle 1) and subsequent doses 6 mg/kg], all on day 1 of a 21-day cycle. Patients who developed cumulative toxicity to cisplatin or docetaxel could continue on trastuzumab as a single agent if progression free. In 2006, 9 (16%) of 55 screened patients had HER2-positive tumors. Best response in five treated patients was one CR, three PR, one SD (control disease 100%). One patient died of an upper gastrointestinal bleed possibly related to study treatment and/or migrating stent. Other grade 3/4 toxic effects included peripheral neuropathy, abdominal cramping, and neutropenia (one patient each).

phase III of cisplatin/fluoropyrimidine vs cisplatin/fluoropyrimidine/trastuzumab: ToGA trial. The ToGA is a multicenter, international trial to be conducted at 130 centers in Europe, Russia, Japan, Korea, China, Taiwan, Australia, Central and South America, South Africa, India, and Turkey. This study is evaluating the combination of trastuzumab with standard fluoropyrimidine plus cisplatin chemotherapy in advanced HER2-positive gastric cancer in first-line setting vs the same chemotherapy alone. Regarding the chemotherapy, investigators can choose between 5-fluorouracil/cisplatin and capecitabine/cisplatin. Patients will be treated with six cycles of chemotherapy in both treatment arms. Patients in the experimental arm will continue to be treated with trastuzumab until disease progression. The primary objective is to compare OS in both arms, and the secondary objectives are to compare progression-free survival, time to progression, overall response rate, control disease, duration of response, and quality of life between the two treatment arms. So far, 400 out

Table 3. Clinical trials of trastuzumab-based therapy

Author	n	Phase	Line	Schedule	ORR	Toxicity	Comments
Cortés-Funes et al. [58]	21	II	First	Cisplatin 75 mg/m ² d1; trastuzumab 8 mg/kg first cycle, 6 mg/kg every 3 w	35%	No grade IV	Preliminary results
Nicholas et al. [59]	5	II	First	Cisplatin 75 mg/m ² d1; docetaxel 75 mg/m ² d1; trastuzumab 8 mg/kg first cycle, 6 mg/kg every 3 w	1 CR, 3 PR, 1 SD	–	–
ToGA	584	III	First	Cisplatin/fluoropyrimidine; cisplatin/fluoropyrimidine/trastuzumab	–	–	Ongoing
Reh et al. [60]	3	II	Second	Trastuzumab monotherapy	–	–	–

ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; w, week; d, day.

of 584 patients have been randomized and first efficacy data are expected in 2009.

second-line setting

To our knowledge, only one trial is evaluating the efficacy and safety of trastuzumab monotherapy (loading dose 4 mg/kg and then weekly doses of 2 mg/kg) in patients with locally advanced or metastatic HER2-positive gastric cancer who progressed under a previous platinum-based or 5-fluoropyrimidine-based chemotherapy [60]. At the end of April 2006, only 3 out of 33 patients were IHC 3+ and thus eligible for trastuzumab therapy.

conclusions

Gastric cancer is the second leading cause of cancer mortality in the world. In Western countries, most of the patients are diagnosed when the tumor is at an unresectable stage. In this setting, systemic chemotherapy is the main treatment option. Although many single agents and combinations are active in metastatic disease, there is no internationally accepted standard of care and survival remains poor. Therefore, new therapeutic strategies are needed. There is mounting evidence of the role of HER2 overexpression in patients with gastric cancer, and it has been solidly correlated to poor outcomes and a more aggressive disease. Regarding pathologic variables, a higher rate of HER2 expression in intestinal histologic type than in diffuse type has consistently been reported. Also, GEJ cancers express HER2 with more frequency than gastric cancers do. In experimental models, trastuzumab suppresses the growth of human gastric cancer with HER2 overexpression *in vitro* and *in vivo*. As results of these preclinical data, several clinical trials are exploring in different settings and with diverse designs the potential of anti-HER2 therapies in gastric cancer patients. The results of these studies will contribute to a better knowledge of the efficacy and tolerance of trastuzumab-based therapy in HER2-positive gastric or GEJ cancers.

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