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ORIGINAL ARTICLE

Correlation of human epidermal growth factor receptor 2 expression with clinicopathological characteristics and prognosis in gastric cancer

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Abstract

AIM: To investigate human epidermal growth factor receptor 2 (*HER2*) gene amplification and protein expression in Chinese patients with resectable gastric cancer and the association with clinicopathological characteristics and survival.

METHODS: One hundred and ninety-seven gastric cancer patients who underwent curative surgery procedures were enrolled into this study. *HER2* gene amplification and protein expression were examined using fluorescence *in-situ* hybridization (FISH) and immunohistochemistry (IHC) analysis on formalin-fixed paraffin-embedded gastric cancer samples from all patients. For scoring, Hofmann's HER2 gastric cancer scoring system was adopted. All cases showing IHC3+ or FISH positivity were defined as HER2 positive. Patient clinicopathological data and survival information were collected. Finally, χ^2 statistical analysis was performed to analyze the HER2 positivity rate amongst the subgroups with different clinicopathological characteristics including; gender, age, tumor location, Lauren classification, differentiation, TNM staging, depth of invasion, lymph node metastases and distant metastasis. The probability of survival for different subgroups with different clinicopathological characteristics was calculated using the Kaplan-Meier method and survival curves plotted using log rank inspection.

RESULTS: According to Hofmann's HER2 gastric cancer scoring criteria, 31 cases (15.74%) were identified as *HER2* gene amplified and 19 cases (9.64%) were scored as strongly positive for HER2 membrane staining (3+), 25 cases (12.69%) were moderately positive (2+) and 153 cases (77.66%) were HER2 negative (0/1+). The concordance rate between IHC and FISH analyses was 88.83% (175/197). Thirty-six cases were defined as positive for *HER2* gene amplification and/or protein expression, with 24 of these cases being eligible for Herceptin treatment according to United States recommendations, and 29 of these cases eligible according to EU recommendations. Highly consistent results were detected between IHC3+, IHC0/1 and FISH (73.68% and 95.42%), but low consistency was observed between IHC2+ and FISH (40.00%). The positivity rates in intestinal type and well-differentiated gastric cancer were higher than those in diffuse/mixed type and poorly-differentiated gastric cancer respectively (28.57% *vs* 13.43%, $P = 0.0103$; 37.25% *vs* 11.64%, $P < 0.0001$), but were not correlated with gender, age, tumor location or TNM stage, depth of invasion, lymph node metastases and distant metastasis. In poorly-differentiated gastric cancer patients, those without lymph node metastasis showed a higher HER2 positivity rate than those with lymph node metastasis (26.47% *vs* 7.14%, $P = 0.0021$). This association was not present in those

patients with well-differentiated gastric cancer (28.57% *vs* 43.33%, P = 0.2832). Within our patient cohort, 26 cases were lost to follow-up. The median survival time for the remaining 171 patients was 18 mo. The median survival times of the HER2 positive and negative groups were 17 and 18.5 mo respectively. Overall survival was not significantly different between HER2-positive and negative groups (χ^2 = 0.9157, P = 0.3386), but in patients presenting well-differentiated tumors, the overall survival of the HER2-positive group was significantly worse than that of the HER2-negative group (P = 0.0123). In contrast, patients with poorly differentiated and diffuse/mixed subtype gastric cancers showed no significant differences in overall survival associated with HER2. Furthermore, the median survival time of the HER2 positive group did not show any statistically significant differences when compared to the subgroups of gender, age, tumor location, TNM classification, lymph node metastases and distant metastasis.

CONCLUSION: Patients with intestinal type gastric cancer (GC), well-differentiated GC and poorly-differentiated GC without lymph node metastasis, may all represent suitable candidates for targeted therapy using Herceptin.

Key words: Gastric cancer; Human epidermal growth factor receptor 2; Gene amplification; Protein expression; Clinicopathological characteristics

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INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) is a 185-kDa transmembrane tyrosine kinase receptor[1] and its gene amplification and protein overexpression play an important role in the proliferation, apoptosis, adhesion, angiogenesis and aggressiveness of many solid tumors[2], including; breast[3], colon[4], bladder[4], ovarian[5], uterine cervix[6], esophageal[7] and gastric cancer.

Herceptin (trastuzumab) has been approved[8] in the European Union and the United States for use in combination with 5-fluorouracil (5-FU) or capecitabine plus cisplatin for the first-line treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction according to the results of the 2010 trastuzumab for gastric cancer (ToGA) trial. However, precise patient inclusion criteria for Herceptin treatment is still not fully defined due to the lack of a standardized HER2 scoring system for gastric cancer[9,10]. For a clinician, defining the relationships between HER2 and clinicopathological characteristics can help to select suitable candidates.

Our study aimed to investigate the relationship between *HER2* gene amplification and protein overexpression in resectable gastric cancer patients and determine any correlations with relevant clinicopathological characteristics. Furthermore, we explored the influence of HER2 on disease prognosis in gastric cancer patients. Our study was conducted with a view towards the future introduction of Herceptin targeted therapy for the treatment of gastric cancer patients.

MATERIALS AND METHODS

Patients and tissue specimens

From July 2009 to January 2012, 197 gastric cancer patients who underwent curative surgery at Renji hospital, Shanghai Jiaotong University were enrolled into our study. Formalin-fixed, paraffin-embedded samples of tumors and corresponding normal stomach tissues from 197 gastric cancer patients were evaluated for HER2 protein and gene amplification using immunohistochemistry (IHC) and fluorescence *in-situ* hybridization (FISH) analysis. None of the patients had undergone prior preoperative radiation, chemotherapy or targeted therapy.

The study included 65 women and 132 men, with ages ranging from 22 to 88 years. The median age was 62 years. The tumor sample characteristics of all 197 cases are shown in Table 1. Of all the tumors examined, 31 (15.74%) were located in the cardiac region, 42 (21.32%) in the body, and 122 (61.93%) in the pylorus. The majority (98.98%) of the samples were primary tumors with only 2 recurrent tumors identified. According to Lauren classification, 63 (31.98%) tumors were intestinal-type and 134 (68.02%) were diffuse-type or mixed-type carcinomas. Poorly differentiated tumors (grades Ⅰ and Ⅱ) comprised 25.89%, whilst 74.11% of tumors were moderately differentiated (grades Ⅲ and Ⅳ). TNM classification revealed that 13 cases were stage Ⅰ (6.60%), 46 were stage Ⅱ (23.35%), 98 were stage Ⅲ (49.75%) and 40 were stage Ⅳ (20.30%). Postoperative follow-up ended in April, 2012.

FISH detection for HER2 gene amplification

FISH was conducted with the HER2 DNA Probe Kit (Invitrogen™ by Life Technologies) according to the manufacturer's instructions. Four-μm-thick sections were baked overnight at 56 ℃, deparaffinized in three 10 min changes of xylene and then rehydrated through two 5-min changes of 100% ethanol. The slides were then reduced for 18 min in SPOT-Light tissue pretreatment solution at > 98 ℃, and briefly washed in 3 × PBS at room temperature. The slides were then incubated for 16 min in enzyme reagent solution at 37 ℃ and washed in 3 × PBS at room temperature, dehydrated through 70%, 85%, and 100% ethanol, and allowed to air dry. After open air drying, the HER2 DNA probe kit (PathVysion HER2 DNA Probe Kit, Abbott Laboratories) which was denatured at

Table 1 Correlation of human epidermal growth factor receptor 2 expression with clinicopathological characteristics *n* (%)

Clinicopathological characteristics	*n*	HER2		χ^2	*P* value
		Positive	Negative		
Sex				1.2736	0.2591
Male	132	27 (20.45)	105 (79.55)		
Female	65	9 (13.85)	56 (86.15)		
Age (yr)				1.3056	0.2532
< 60	88	13 (14.77)	75 (85.23)		
⩾ 60	109	23 (21.10)	86 (78.90)		
Tumor site[1]				0.0409	0.9798
Cardiac	31	6 (19.35)	25 (80.65)		
Body	42	8 (19.05)	34 (80.96)		
Pylorus	122	22 (18.03)	100 (81.97)		
Lauren classification				6.5759	0.0103
Intestinal	63	18 (28.57)	45 (71.43)		
Diffuse/mixed	134	18 (13.43)	116 (86.57)		
Tumor differentiation				16.6003	< 0.0001
Well-differentiated	51	19 (37.25)	32 (62.75)		
Poorly-differentiated	146	17 (11.64)	129 (88.36)		
TNM classification				0.6754	0.879
Ⅰ	13	2 (15.38)	11 (84.62)		
Ⅱ	46	7 (15.22)	39 (84.78)		
Ⅲ	98	20 (20.41)	78 (79.59)		
Ⅳ	40	7 (17.50)	33 (82.50)		

[1]Two remnant samples were not included. HER2: Human epidermal growth factor receptor 2.

79 ℃ for 6 min, was applied onto each slide, a cover slip was added and then sealed with rubber cement. After 16 to 18 h of hybridization at 37 ℃, the slides were washed with 73 ℃ preheated post hybridization buffer for 5 min and dehydrated through 70%, 85% and finally 100% ethanol. After air drying, the slides were counter-stained with 14 μL diamidino-phenyl-indole, cover slips applied and then slides chilled for 30 min at 4 ℃. Finally, the slides were observed through a fluorescence microscope (OLYMPUS BX61).

Immunohistochemical staining

HER2 IHC analysis was performed on 4 μm thick tissue sections. Briefly, after deparaffinization and rehydration steps, the tissue samples were incubated in antigen retrieval solution at 99 ℃ for 40 min. Endogenous peroxidase activity was quenched by 5 min incubation with hydrogen peroxide. Sections were then incubated with HER2 antibody (Herceptest™, DAKO) for 30 min. Both the primary and secondary antibodies against human HER2 protein were applied for 30 min at room temperature and then the immunocomplexes were visualized with diaminobenzidine for 10 min and placed under a cover slip. Finally, the slides were viewed using light microscopy (LEICA DM2500).

Results scoring

An absolute *HER2* gene copy number lower than 6 or a HER2/Chr17 ratio of less than 2 was considered HER2 negative, whilst cases showing average gene copy numbers of HER2 ⩾ 6 or a gene/CEN17 fluorescence ratio ⩾ 2 were considered positive for gene amplification.

Table 2 Immunochemistry-fluorescence *in situ* hybridization concordance *n* (%)

FISH	IHC				Total
	3+	2+	1+	0	
Positive	14	10	7	0	31 (15.74)
Negative	5	15	21	125	166 (84.26)
Total	19 (9.64)	25 (12.69)	28 (14.21)	125 (63.45)	197

IHC: Immunochemistry; FISH: Fluorescence *in-situ* hybridization.

Additionally, tight gene clustering of HER2 signals was also defined as gene amplification. The above criteria are based on Hofmann's criteria in gastric cancer[9].

In the present study, the IHC score criteria on human gastric cancer also followed Hofmann's criteria[9]: no staining or < 10% tumor cell positive staining as 0/negative; faintly or barely perceptible staining on > 10% tumor cell membrane as 1+/negative; weak to moderate positive staining on > 10% tumor cells as 2+/(equivocal) positive; cohesive moderate to strong staining on the membrane will be scored as 3+/positive. All cases with IHC3+ or FISH positivity were defined as HER2 positive.

Statistical analysis

χ^2 statistical analysis was performed to assess the HER2 positivity rate amongst the subgroups with different clinicopathological characteristics. The probability of survival for different subgroups was calculated using the Kaplan-Meier method and the survival curves plotted using log rank inspection. All statistics were performed using 2-sided analysis, with a significance level of $P < 0.05$, using the "SAS9.13" statistical software package.

RESULTS

HER2 gene amplification and protein expression

The FISH and IHC analysis results for all 197 gastric cancer tissues are shown in Table 2. According to Hofmann's HER2 FISH scoring criteria, 31 cases (15.74%) were identified as *HER2* gene amplified and the other 166 cases (84.26%) were *HER2* gene amplification negative (Figure 1). Of the 197 samples examined by IHC (following Hofmann's criteria), 19 cases (9.64%) were scored as strongly positive for HER2 membrane staining (3+), 25 cases (12.69%) were moderately positive (2+), and 153 cases (77.66%) were HER2 negative (0/1+) (Figure 2).

The concordance rate between IHC and FISH analyses was 88.83% (175/197). Thirty-six cases were defined as HER2 positive and 24 cases were suitable for Herceptin treatment according to the recommendations of the United States[11]. However, when applying European Union[11] recomnmendations for Herceptin usage, 29 cases were identified as eligible for Herceptin treatment. This difference underscores the requirement for standardized and more precise eligibility criteria for correct identification of patients who are eligible for HER2 targeted therapy.

Of the 31 FISH-positive cases, 14 cases (45.16%)

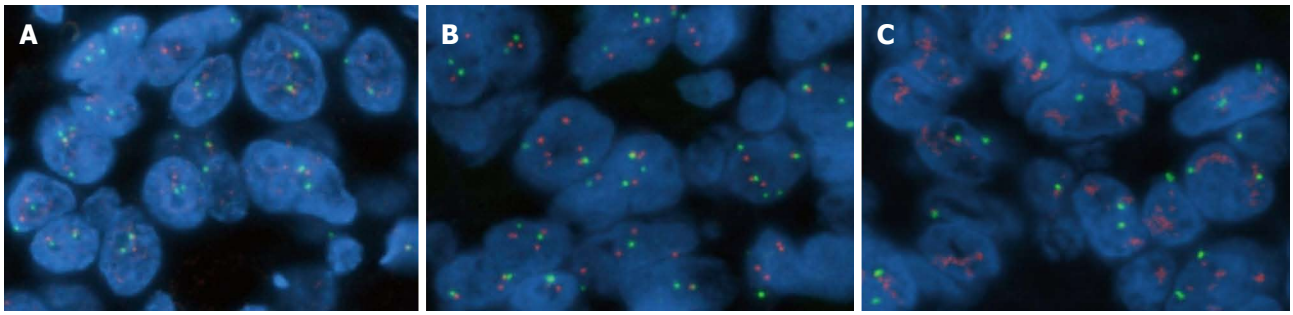

Figure 1 Fluorescent *in-situ* hybridization analysis of human epidermal growth factor receptor 2 gene amplification (× 600). A: Normal human epidermal growth factor receptor 2 (*HER2*) gene expression: Red signals (*HER2* gene), green signals [chromosome enumeration probe 17 (CEP17)], blue signals (nuclei lining dye); B: Positive *HER2* gene amplification: HER2:CEP17 > 2; C: Positive *HER2* gene amplification: HER2:CEP17 > 2 with clear red cluster signals observed.

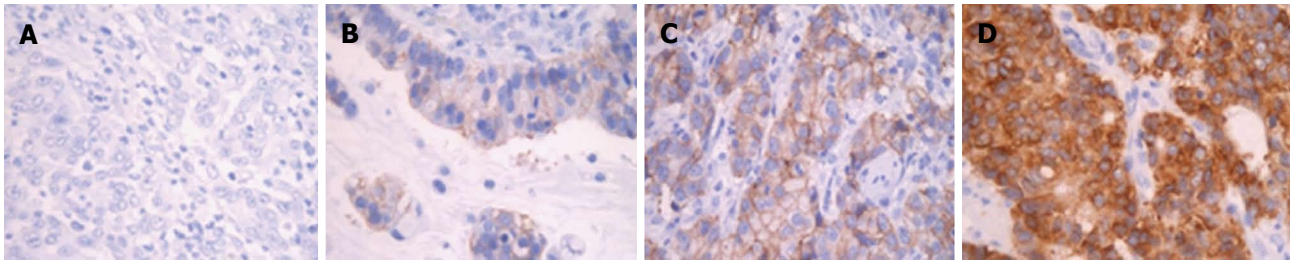

Figure 2 Immunohistochemical analysis of human epidermal growth factor receptor 2 protein expression (× 200). A: Immunohistochemical (IHC) 0: No staining on tumor cell membrane; B: IHC1+: Faintly perceptible staining on > 10% tumor cell membrane; C: IHC2+: Moderate staining on > 10% tumor cell membrane; IHC3+: Strong staining on > 10% tumor cell membrane.

Table 3 Correlation of human epidermal growth factor receptor 2 expression with tumor node metastasis staging *n* (%)

Clinicopathological characteristics	*n*	HER2		χ^2	*P* value
		Positive	Negative		
T				0.5782	0.4470
T1-T2	26	6 (23.08)	20 (76.92)		
T3-T4	171	29 (16.96)	142 (84.04)		
N				4.6274	0.2012
N0	55	8 (14.55)	47 (85.45)		
N1	83	20 (24.10)	63 (75.90)		
N2	33	5 (15.15)	28 (84.85)		
N3	26	2 (7.69)	24 (92.31)		
M				0.0000	1.0000
M0	185	33 (17.84)	152 (82.16)		
M1	12	2 (16.67)	10 (83.33)		

HER2: Human epidermal growth factor receptor 2.

were IHC3+ with a 100% concordance between IHC3+ and FISH, and 10 (32.26%) cases were IHC2+. None of the IHC 0 tumors demonstrated FISH amplification, and only 7 tumors in the IHC1+ group were found to be FISH positive with a ratio of 22.58%. High consistency results was detected between IHC3+, IHC0/1, and FISH scores (73.68% and 95.42%), but low consistency was observed between IHC2+ and FISH (40.00%).

Correlation of HER2 with clinicopathological characteristics

Significantly different HER2 positivity rates were observed when comparing intestinal-type gastric cancers with diffuse/mixed-type cancers (28.57% *vs* 13.43%, $P = 0.0103$), and well-differentiated cases with poorly-differentiated cases (37.25% *vs* 11.64%, $P < 0.0001$). No relationship was observed between the HER2 positivity rate and sex, age, tumor site and TNM GC classification ($P > 0.05$; Table 1). Furthermore, within the subgroups, no relationship was observed between HER2 positivity and depth of invasion, lymph node metastasis or distant metastasis (Table 3).

Within the poorly-differentiated gastric cancer patient group, those without lymph node metastasis showed a higher HER2 positivity rate than those with lymph node metastasis (26.47% *vs* 7.14%, $P = 0.0021$). This association was not observed in the well-differentiated gastric cancer patient group (28.57% *vs* 43.33%, $P = 0.2832$).

Survival analysis

Of our 197 gastric cancer patients, 26 cases were lost in follow-up. The median survival time for the remaining 171 patients was 18 mo (range: 0-33 mo). During the follow-up time, 60 deaths occurred (35.09%), 57 of which were disease-related. One patient died of perioperative pulmonary infection, and two cases died of heart disease and multiple organ failure, respectively.

The median survival time of the HER2 positive (29 cases) and negative groups (142 cases) was 17 mo and 18.5 mo, respectively. Nevertheless, the HER2 positive gastric cancer patients did not show statistically significant reductions in mean survival times, nor lower 1-year or 2-year survival rates. Furthermore, no statistically significant differences were observed in overall survival

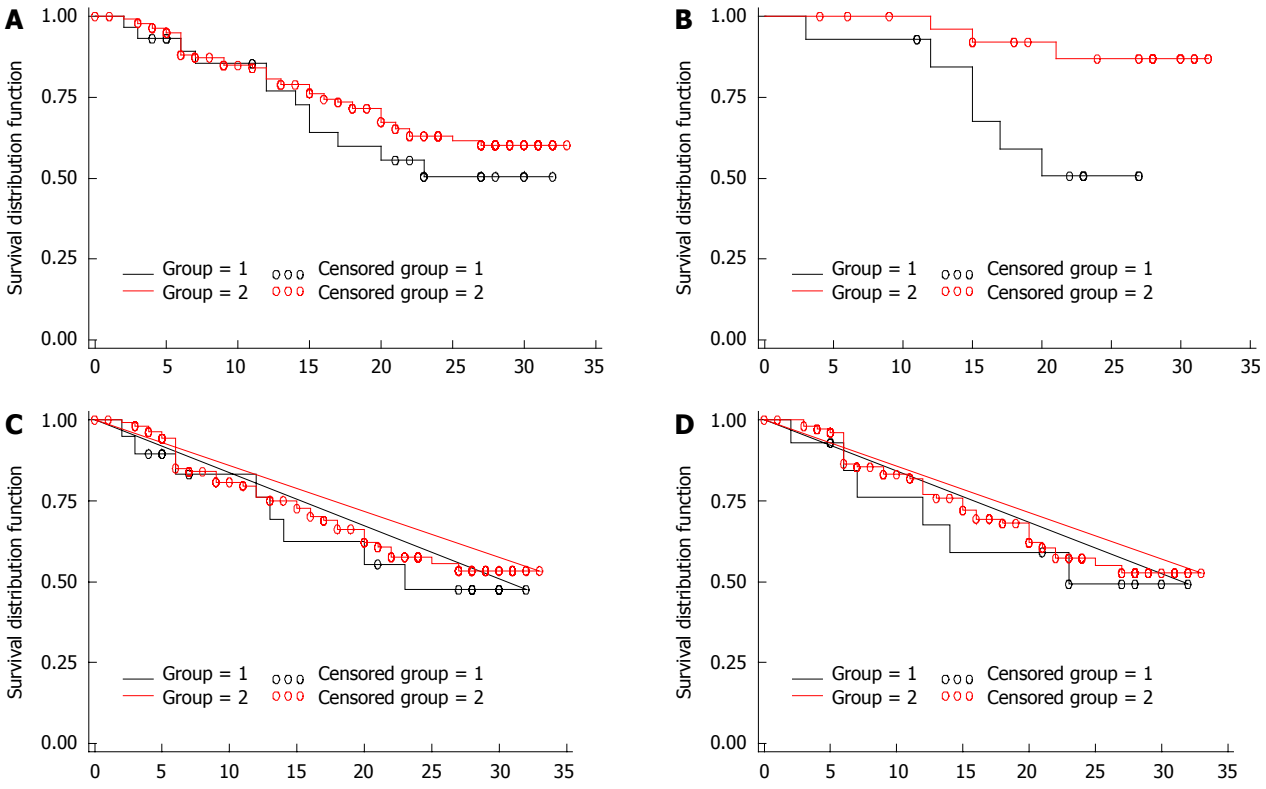

Figure 3 Kaplan-Meier survival analysis. A: Overall survival curves of 171 gastric cancer patients according to human epidermal growth factor receptor 2 (HER2) detection (P = 0.3386); B: Survival curve of patients with well differentiated gastric cancer according to HER2 expression (P = 0.0123); C: Survival curve of patients with poorly differentiated gastric cancer according to HER2 expression (P = 0.0988); D: Survival curve of patients with the diffuse/mixed type gastric cancer according to HER2 expression (P = 0.6623).

times between the HER2 positive and negative groups (χ^2 = 0.9157, P = 0.3386; Figure 3A).

Within the well differentiated gastric cancer patient group, patients with HER2 tumor positivity had poorer outcomes than those with HER2 negative tumors. The well differentiated HER2 positive patient group exhibited shorter mean survival time (18.5 mo *vs* 27.5 mo) and lower 1-year and 2-year survival rates compared to the HER2 negative group (84.42% *vs* 96.00%; 50.65% *vs* 86.89%; P = 0.0123; Figure 3B). The median survival time of the HER2 positive group did not show any statistical associations when compared to the subgroups of sex, age, tumor site, TNM classification, depth of invasion, lymph node metastases and distant metastasis in gastric cancer (Table 4). Within the poorly differentiated and diffuse/mixed type gastric cancer patient groups, no statistically significant differences were observed between the HER2 positive and HER2 negative groups (Figure 3C and D).

DISCUSSION

HER2 gene amplification and protein overexpression in gastric cancer were first reported in 1986[12,13]and have since been confirmed by numerous studies, highlighting ranges in both *HER2* gene amplification rates from 16%-27.1% by FISH analysis and HER2 protein overexpression from 8.2%-53.4% by IHC analysis. The variability within these results is likely due to several factors including sample size, study design and differences in geographic location[14]. However, the most important variability factor is likely a consequence of having no standardized HER2 test and scoring criteria[15]. In the present study, both FISH and IHC scoring criteria followed that of Hofmann[9] which is considered to be the most appropriate HER2 scoring system in human gastric cancer. Furthermore, to ensure the reliability of our results, we followed the guidelines on HER2 detection in breast cancer, recommended by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP)[16] and used the test kit certified by the United States Food and Drug Administration.

Herceptin (trastuzumab) is a recombinant human monoclonal antibody designed to target and block the function of HER2 by directly binding to the extracellular domain of the receptor[1,17]. It has been used for the treatment of HER2 overexpressing breast cancer for more than 10 years and was approved by the European Medicines Agency[18] in 2010 for use in combination with capecitabine or 5-FU and cisplatin for metastatic gastric or GE junction cancers, based on data from the 'ToGA" clinical trial. The exact anti-tumor mechanism of Herceptin is not fully understood, however some mechanisms have been postulated[17,19-23] including interruption of HER2 mediated cell signaling pathways and cell cycle progression; induction of antibody-dependent cell-mediated cytotoxicity and apoptosis; induction of

Table 4 Relationship of different clinicopathological characteristics and prognosis

Clinicopathological characteristics	HER2 positive			HER2 negative			χ^2	*P* value
	Median survival time (mo)	1-year survival rate	2-year survival rate	Median survival time (mo)	1-year survival rate	2-year survival rate		
Sex								
Male	20	74.34%	50.18%	20	83.96%	69.00%	2.2591	0.1328
Female	10	100.00%	50.00%	16.5	74.50%	51.79%	0.0182	0.8927
Age (yr)								
≤ 60	23	100.00%	57.14%	20	80.54%	61.81%	0.0104	0.9186
> 60	15	67.55%	49.13%	18	80.62%	64.35%	1.6356	0.2009
Tumor site								
Cardiac	19	66.67%	50.00%	15	69.51%	49.15%	0.0494	0.8242
Body	16.5	62.50%	62.50%	14	67.80%	44.07%	0.1561	0.6927
Pylorus	17	85.56%	46.67%	20	87.00%	73.25%	2.3295	0.1269
Lauren classification								
Intestinal	17	84.85%	50.91%	27	89.17%	76.53%	2.3604	0.1244
Diffues/mixed	14	67.53%	49.24%	16.5	76.99%	57.24%	0.1907	0.6623
Tumor differentiation								
Well-differentiated	18.5	84.42%	50.65%	27.5	96.00%	86.89%	6.2701	0.0123
Poorly-differentiated	14	67.88%	49.49	17	76.56%	56.71%	0.0988	0.7532
TNM classification								
Ⅰ and Ⅱ stages	18.5	68.57%	57.14%	21.5	93.60%	79.20%	2.9813	0.0842
Ⅲ and Ⅳ stages	17	82.59%	45.88%	16.5	73.32%	54.12%	0.0263	0.8711
T								
T1-T2	17	66.67%	66.67%	28	100.00%	92.31%	3.4587	0.0629
T3-T4	15	91.30%	46.99%	17	77.47%	58.26%	0.2953	0.5869
N								
N0	14	68.57%	51.43%	21	90.46%	74.98%	2.0667	0.1505
N1-N3	18.5	79.19%	49.49%	17	75.73%	57.27%	0.0531	0.8177
M								
M0	17	78.67%	54.69%	20	84.41%	66.01%	0.7842	0.3757
M1	11.5	50.00%	0.00%	5	0.00%	0.00%	0.5900	0.4424

HER2: Human epidermal growth factor receptor 2.

anti-angiogenesis effects and increasing receptor turnover by endocytosis. As clinical surgeons, we should be readily and accurately able to identify which patients are suitable for Herceptin treatment. An accurate and reliable HER2 scoring system, together with clinical information, may help us to better determine whether a gastric cancer patient is a potential candidate for targeted therapy using Herceptin.

The relationship between *HER2* gene amplification and protein expression in gastric cancer patients is controversial[24,25]. Nevertheless, more recent studies have reported a high concordance between gene amplification and protein overexpression using FISH and IHC approaches[11,26,27]. Indeed, the ToGA trial[28] (which recruited the largest population of gastric cancer patients to date-3807) reported a HER2 FISH and IHC concordance rate of 87.5%, and further reported that HER2 IHC3+ cases were almost all entirely *HER2* gene amplified (97.5% of cases). However, 22.5% of HER2 FISH positive cases in the ToGA trial were HER2 IHC negative, a finding which differs from the situation observed in breast cancer, where almost all HER2 IHC 0/1+ samples are HER2 FISH negative[14]. In our study, the overall HER2 positive rate (FISH and IHC combined) was 18.27% while 15.74% of cases showed *HER2* gene amplification by FISH and 9.64% of patients showed HER2 protein overexpression by IHC analysis. The concordance between the two detection methods was 88.83%. Of the 31 FISH-positive cases, 14 cases (45.16%) were IHC3+, with a 100% concordance between IHC3+ and FISH, and 10 (32.26%) cases were IHC2+. None of the IHC0 tumors showed FISH amplification, and only 7 tumors in the IHC1+ group were found to be FISH positive with a ratio of 22.58%. A high degree of data consistency was observed between IHC3+ and IHC0/1 with FISH (73.68% and 95.42%); however, low scoring consistency was observed between IHC2+ and FISH (40.00%). Thus, our data highlights the need and importance of further clarifying the relationship between *HER2* gene amplification and protein overexpression in gastric cancer.

In our study, no relationship was observed between HER2 positivity and sex, age and TNM classification ($P > 0.05$). However, intestinal-type and well-differentiated gastric cancer cases showed a higher HER2 positive rate than diffuse/mixed-type and poorly-differentiated cancer cases. This finding is in keeping with similar data from the ToGA trial and other published studies[29,30]. Of interest, the ToGA trial reported a higher HER2 positivity rate in GE junction cancers compared to other gastric cancers (33.2% *vs* 20.9%, $P < 0.001$)[17]. Our study, as well as that of another group[31], showed no statistically significant difference between HER2 positivity and the gastric tumor site. Within the poorly-differentiated gastric cancer patient group, those patients without lymph node

metastasis showed a higher HER2 positivity rate when compared to those with lymph node metastasis (26.47% *vs* 7.14%, $P = 0.0021$). No difference in HER2 positivity was observed, however, when comparing lymph node metastasis status in the well-differentiated gastric cancer patient group (28.57% *vs* 43.33%, $P = 0.2832$). The underlying molecular mechanisms behind the varying HER2 positivity rates in the different histological GC subtypes are clearly complex and require further investigation.

The role of HER2 as a prognostic factor in gastric cancer has been controversial due to significant differences in historical study results. More recent studies, however, indicate that HER2 is a poor prognostic factor in gastric cancer patients[32-35], especially those with liver metastases[36]. Whilst our study did not show any correlation between HER2 status and overall survival, patients with well-differentiated HER2 positive tumors showed poorer survival times compared to patients with HER2 negative tumors. We speculate that HER2 status has a mild impact on gastric cancer patient survival and may not constitute an independent prognostic factor in gastric cancer patients. Clearly, further research is required to explain the impact of HER2 on development and prognosis of gastric cancer.

In conclusion, an accurate and standardized scoring system for HER2 expression in gastric cancer patients is of clear importance and utility in the optimal selection of patients for Herceptin therapy. Our studies highlight intestinal-type, well-differentiated and poorly-differentiated gastric cancer patients without lymph node metastasis as the three main candidate patient groups for targeted therapy using Herceptin. Finally, we advocate further detailed research on the mechanism(s) through which HER2 expression drives progression of gastric cancer and consideration of additional studies to explore the role of HER2 as an independent prognostic factor.

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COMMENTS

Background

Gastric cancer (GC) is one of the most prevalent cancers worldwide, with poor prognosis. Herceptin (trastuzumab) can improve overall survival without compromising safety in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic gastric cancer. However, a standardized HER2 scoring system is still required. Studies on the correlation of HER2 and clinicopathological characteristics could help clinicians to optimally select suitable candidates for targeted therapy using Herceptin.

Research frontiers

HER2 inhibition is playing a significant role as a new treatment option for gastric cancer. Numerous countries have approved the use of Herceptin for the treatment of gastric cancer and increasingly, HER2 has become a "hot" research topic. An accurate and reliable HER2 scoring system is necessary to select suitable candidates for Herceptin targeted therapy.

Innovations and breakthroughs

To date, there have been limited studies to determine any correlations of HER2 expression with clinicopathological characteristics and prognosis in Chinese patients with resectable gastric cancer. Intestinal type gastric cancer patients, well-differentiated gastric cancer patients and poorly-differentiated gastric cancer patients without lymph node metastasis showed a higher HER2 positivity rate and thus could represent ideal candidates for targeted-therapy using Herceptin.

Applications

The study results suggest that an accurate HER2 scoring system plays an important role with clinical significance. Patients with intestinal-type gastric cancer, well-differentiated gastric cancer and poorly-differentiated gastric cancer without lymph node metastasis are ideal candidates for targeted therapy using Herceptin.

Peer review

The paper makes sense to search for the gastric cancer patients in Jiangsu province. The study design is valid and the data is sufficient.

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