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Her-2 neu status in gastric carcinoma in Egyptian patients: The epidemiology and the response to chemotherapy

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Her-2 neu status in gastric carcinoma in Egyptian patients: the epidemiology and the response to chemotherapy

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Background
Gastric cancer is the fourth most commonly diagnosed cancer and the second most common cause of cancer-related death worldwide, affecting one million people per year. Currently, gastric cancer is still the seventh most common cause of cancer-related death in the USA, and the prognosis of advanced gastric cancer remains poor.

Objectives
The aim of this study was to assess the frequency of *Her-2* overexpression and amplification in Egyptian patients with gastric/gastroesophageal adenocarcinoma, in correlation with tumor histology, grade, size, and location (cardia vs. noncardia).

Patients and methods
This study included 39 eligible patients with pathologically proven gastric/gastroesophageal carcinoma presented to Menoufia University Oncology Hospital, Alexandria Military Hospital, from January 2012 until the end of June 2013.

Results
It was found that the mean age was 55.3 years. There was slightly higher incidence in the male population (51.3%). All of them had tumors of diffuse histopathological type. Stage at presentation was as follows: localized, one (2.6%); locally advanced, 20 (51.3%); and metastatic, 18 (46.2%). Her-2 was found to be overexpressed in four out of 39 patients (10.3%). *Her-2*-negative patients had a significantly longer overall survival (9 months in Her-2 negative-patients vs. 4 months in Her-2-positive patients) ($P = 0.01$). Progression-free survival (PFS) was significantly prolonged in *Her-2*-negative patients. *Her-2*-negative patients had a PFS of 8 months, versus only 4 months in *Her-2*-positive patients ($P = 0.01$). Median survival and PFS in locally advanced disease were significantly affected by the *Her-2* status ($P = 0.02$). Neither median survival ($P = 0.8$) nor PFS ($P = 0.5$) was affected in metastatic disease.

Conclusion
Her-2 is a prognostic factor in a small cohort of Egyptian patients with gastric/gastroesophageal carcinoma.

Keywords:
gastric cancer, *Her-2*, survival

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Introduction

Gastric cancer is the fourth most commonly diagnosed cancer and the second most common cause of cancer-related death worldwide, affecting one million people per year [1,2]. Currently, gastric cancer is still the seventh most common cause of cancer-related death in the USA, and the prognosis of advanced gastric cancer remains poor [3].

In 2006, Middle East Cancer Consortium (MECC) had published a monograph presenting the information on the incidence of gastric cancer for populations in the Middle East from 1996 to 2001. Egypt had the lowest incidence in the region, with 2.9. US SEER (Surveillance, Epidemiology, and End Results) incidence was 5.3 for the same years. These rates are 5–15 times lower than that in Japan, where the overall rate was more than 50 [4].

Development of gastric carcinoma is a multistep and multifactorial process. Although the intestinal type of gastric cancer is often related to environmental factors such as *Helicobacter pylori* infection, diet, and lifestyle, the diffuse type is more often associated with genetic abnormalities. Recent advances in molecular medicine have not only shed light on the carcinogenesis of gastric cancer but also offered novel approaches on prevention, diagnosis, and therapeutic intervention [4].

Generally, for early stage disease, radical surgery represents the standard form of therapy that has curative intent. However, the incidences of local failure in the tumor bed and regional lymph nodes, and

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distant failures through hematogenous or peritoneal routes, remain high. As such, adjuvant external-beam radiation therapy with combined perioperative chemotherapy has been evaluated. For the advanced stages, chemotherapy is the main palliative treatment modality, with modest results [5].

Progress was recently made, as treating Her-2-Neu-overexpressing gastric cancers with trastuzumab was found to significantly improve survival, as proved by the ToGA trial. This trial compared the addition of trastuzumab to cisplatin/5-fluorouracil with chemotherapy alone. The median progression-free survival (PFS) was 6·7 months [95% confidence interval (CI) 6–8] in the trastuzumab plus chemotherapy group compared with 5·5 months [5,6] in the chemotherapy-alone group (hazard ratio 0·71, 95% CI 0.59–0.85; $P = 0·0002$) [6].

In this study, we studied the incidence of Her-2/T2A expression in gastric and gastroesophageal adenocarcinoma, and their correlation with tumor histology, grade, size, and location (cardia vs. noncardia) in Egyptian patients as the primary objective.

The secondary objective was to examine the response rate and PFS of gastric/gastroesophageal cancers to class different lines of treatment in view of the Her-2/T2A overexpression.

Patients and methods

This study included 39 eligible patients with pathologically proven gastric/gastroesophageal carcinoma presented to Menoufia University Oncology Hospital, Alexandria Military Hospital, from January 2012 until the end of June 2013. Informed consents were obtained from patients according to Helsinki declaration, and the study was approved by the Ethical Committee.

Eligible patients had their pathology specimens revised for the possibility of immunohistochemical (IHC) assessment of Her-2 overexpression. Patients with approved pathology specimens were staged as follows:

(1) Imaging: abdominopelvic computed tomography and chest computed tomography were performed.
(2) Laboratory studies: CEA, CA19.9, complete blood picture, transaminases, bilirubin, creatinine, and urea levels were evaluated.
(3) Echocardiography to assess ejection fraction was requested for patients who received cardiotoxic agents (e.g. anthracyclines).

Response to treatment was assessed according to revised RECIST guidelines (version 1.1) (94) as follows:

Complete response

Complete response was defined as disappearance of all target lesions. Any pathological lymph node (whether target or nontarget) must have reduction in short axis to less than 10 mm.

Partial response

Partial response was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive disease

Progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum in the study (this includes the baseline sum if that is the smallest in the study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (note: the appearance of one or more new lesions is also considered progression).

Stable disease

Stable disease was defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while in the study.

PFS and median survival were investigated in this study. PFS was defined as the length of time during and after the treatment of a disease, such as cancer, during which a patient lives with the disease but it does not get worse). Median survival was defined as the amount of time at which 50% of the patients have died and 50% have survived.

Statistical analysis

Data analysis was carried out using SPSS program for Windows, version 20 (SPSS Inc., Chicago, Illinois, USA). Pearson's χ^2-test and Fisher's exact test were used to determine the significance of associations between categorical variables and response. PFS was analyzed using the Kaplan–Meier curves. It was calculated from the date of diagnosis to the date of progression or the date of death (all causes), whichever occurred first; patients who were not progressed at the last follow-up were censored. Two-sided P-value less than 0.05 was considered statistically significant.

Results

We screened 65 patients for eligibility and availability of biopsy specimen for IHC assessment for Her-2.

Thirty-nine patients were eligible, with their pathological specimen found sufficient for IHC.

The mean age was 55.3 years. There was slightly higher incidence in the male population (51.3%). Patients (59%) frequently presented with a performance status of 1. Smokers were a majority (61.5%). The incidence of familial predisposition was low (2.6%); only one (1/39) patient had a family history of gastric carcinoma in a first degree relative (Table 1).

Diffuse histopathological type (Lauren classification) was dominant (100%). Localized disease was rare (only 2.6%), whereas locally advanced was the most common at presentation (51.3%). Metastatic also comprised a high proportion of patients (46.2%). Distal disease was more common compared with proximal disease (59 vs. 41%). Lymph node involvement was very common in 82.1% of cases (Table 2).

Twenty-three patients underwent surgery (58.9%), nine patients received radiotherapy (23.1%), 29 received first-line chemotherapy (74.4%), and 10 patients received second-line chemotherapy (25.6%). Only four patients received best supportive care (10.1%).

Table 1 Patient characteristics

Patient Criterion	Number of patients [*n* (%)]
Age group (years)	
20–30	1 (3)
31–40	5 (13)
41–50	5 (13)
51–60	11 (28)
61–70	13 (33)
71–80	4 (10)
Sex	
Male	20 (51)
Female	19 (49)
Smoking	
No	24 (62)
Yes	15 (38)
Family history	
No	38 (97)
Yes	1 (3)
ECOG	
ECOG 0	7 (18)
ECOG 1	23 (59)
ECOG 2	9 (23)

Table 2 Disease characteristics

Disease Criterion	Number of patients [*n* (%)]
Lauren histopathological type	Diffuse: 39 (100)
	Intestinal: 0 (0)
Stage at presentation	Localized: 1 (2.6)
	Locally advanced: 20 (51.3)
	Metastatic: 18 (46.2)
Site	Proximal: 16 (41)
	Distal: 23 (59)
Lymph node	Positive: 32 (82.1)
	Negative: 7 (17.9)

Her-2-negative patients had nearly equal chance to undergo either a curative surgery (48.6% underwent curative surgery vs. 51.4% who did not). Her-2-positive patient had much lower chance to undergo a curative surgery (only 25% underwent a curative surgery vs. 75% who did not) ($P = 0.37$).

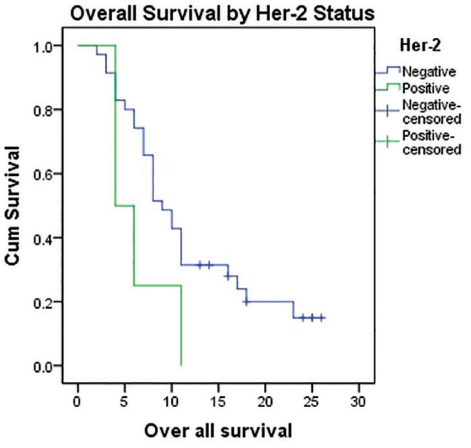
Radiotherapy was infrequently used; only nine patients received radiation, six patients received it as adjuvant radiotherapy (15.4%), and three patients received it as palliation for hematemesis (7.7%). All nine patients had Her-2-negative tumors ($P = 0.5$).

Among the 29 patients who received first-line chemotherapy, G I toxicities occurred in five (12.8%) patients, G II in 18 (46.2%), and G III in six (15.4%) patients. Anthracycline-containing regimens were slightly more associated with G II toxicities (70 vs. 57.9%) compared with nonanthracycline protocols; G III was almost the same (20 vs. 21%) ($P = 0.7$).

Her-2 was found to be overexpressed in four out of 39 patients (10.3%). Her-2-negative patients had a significantly longer overall survival (9 months in Her-2-negative patients versus 4 months in Her-2-positive patients) ($P = 0.01$) (Fig. 1). PFS was significantly prolonged in Her-2-negative patients (8 months in Her-2-negative patients versus only 4 months in Her-2-positive patients) ($P = 0.01$) (Fig. 2).

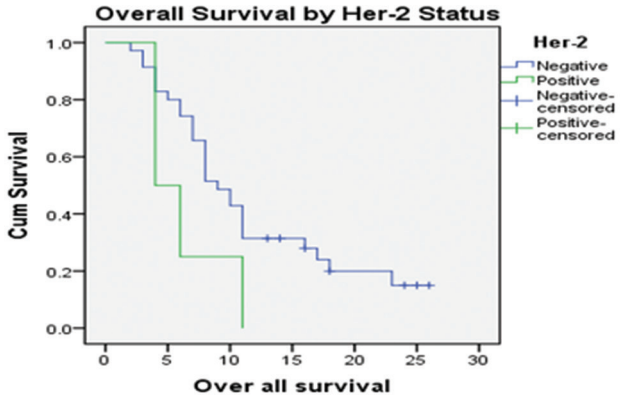
Median survival of locally advanced disease was significantly affected by the Her-2 status, 11 months (95% CI 6.7–15.2) in Her-2-negative patients versus

Figure 1



Correlation between overall survival and Her-2: Kaplan–Meier curve. This Kaplan–Meier curve shows the relation between the median survival time and Her-2 status (9 months for Her-2-negative patients versus 4 months for Her-2–positive patients) ($P = 0.01$).

Figure 2



Correlation between Her-2 status and progression-free survival (PFS): Kaplan–Meier curve. This Kaplan–Meier curve shows the relation between the PFS and Her-2 status. PFS was significantly prolonged in Her-2-negative patients (8 months versus only 4 months in Her-2-positive patients) ($P = 0.01$).

only 4 months in Her-2-positive patients ($P = 0.02$). PFS also was significantly longer in Her-2-negative disease (10 months in Her-2-negative patients versus 3 months in Her-2-positive patients) ($P = 0.02$).

Median survival of metastatic disease was not affected by the Her-2 status, 7 months (95% CI 4.4–9.5) in Her-2-negative patients versus 6 months when Her-2 was overexpressed ($P = 0.8$). Moreover, PFS in metastatic disease was not affected by the Her-2 status, 5 months in Her-2-negative patients (95% CI 4.9–7) versus 4 months in Her-2-positive patients ($P = 0.5$).

Discussion

In our study, we had the aim of correlating the Her-2 overexpression status with the clinical and pathological criteria in 39 Egyptian patients treated for gastric carcinoma. This is the first study in Egypt to discuss such recent issue.

Her-2 was found to be overexpressed in four out of 39 patients (10.3%). Her-2-negative patients had a significantly longer overall survival (9 months in Her-2-negative patients vs. 4 months in Her-2-positive patients) ($P = 0.01$).

The mean age in our study was 49.5 years in Her-2-positive patients, which is younger than those in Her-2-positive patients in the ToGA trial. The mean age was 59.4 years in patients who received chemotherapy alone and 58.4 years in patients who received chemotherapy plus trastuzumab. A Japanese study of 213 patients found a mean age of 71 years in Her-2-positive patients and a mean age of 66.2 years in Her-2-negative patients. In our study, Her-2-negative patients had a mean age of 55.9 years [7]. These results suggest a slight ethnic variation in Her-2 expression profile, with Egyptian patients having Her-2-positive disease in younger ages and Her-2 negative in older ages [8].

In our study, survival of smokers was significantly better when they had Her-2-negative disease ($P = 0.028$); a difference was not revealed among nonsmokers ($P = 0.7$). This may suggest another cutoff to stratify the patients to detect the significance of Her-2 as a prognostic marker.

Her-2 had no significant association with sex or performance status (ECOG). These results are in parallel with those of the 2012 meta-analysis [8], the Chinese study [9], and a recently published retrospective assessment of Her-2 gene amplification in the INT-0116/SWOG9008 trial [10].

In our cohort of patients, we found that Her-2 overexpression is more common in proximal disease (18.8 vs. 4.3% in distal disease = 0.15). Of note, in the pre-ToGA global screening program [11], the *HER2*-positivity rate was similar between Europe (23.6%) and Asia (23.5%). Moreover, HER2-positivity rates were higher in proximal than in distal cancer (33.2 vs. 20.9%; $P < 0.001$), with location/Her-2 incidence coinciding with our cohort. However, as regards the finally included patients in the ToGA trial, we find that most of those Her-2-positive patients (80%) had a distal location, and Asians comprised almost 50% of the ToGA patients, whereas White ethnicity comprised 37% [7].

Our cohort showed an absolute predominance of the diffuse-type (Lauren classification). All 39 patients included had diffuse-adenocarcinoma. This is significantly different from the worldwide data showing intestinal-type predominance with varied degree, ranging from 52 to 82%. In the pre-ToGA screening program [11], HER2-positivity rates were higher in intestinal than in diffuse/mixed cancer (32.2 vs. 6.1–20.4%; $P<0.001$). This is reflected in HER2-positivity rates in countries with the highest intestinal: diffuse cancer ratios [UK 3.4 (HER2 positivity 25.8%); Australia 2.6 (32.8%); Japan 2.8 (27.8%)]. This explains the small percentage of Her-2-positive tumors in the study cohort (10.3%), considering the strong association between intestinal type and *Her- 2* positivity [11]. These findings suggest a particular histomolecular pattern in Egyptian patients with gastric carcinoma, which should be considered in patient stratification and treatment in future clinical trials.

Other molecular events had been recently shown to be of importance in such nonmetastatic disease. Fibroblast growth factor receptor was found to be mutually exclusively amplified with Her-2 in locally advanced gastric carcinoma. Interestingly, the prevalence of fibroblast growth factor receptor 2 amplification was similar between the three included cohorts (UK 7.4%, China 4.6% and Korea 4.2%) [11].

Conclusion

Her-2 seems to be rarely overexpressed in Egyptian patients. These results point out to the shortage of independency of single-standing prognostic factors in gastric carcinoma. It also obviates the need of combining more than one molecular event in the prognostication process in gastric carcinoma.

Conflicts of interest

There are no conflicts of interest.

References

1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; **127**:2893–2917.

2 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; **61**:69–90.

3 Hu B, El Hajj N, Sittler S, Lammert N, Barnes R, Meloni-Ehrig A. Gastric cancer: classification, histology and application of molecular pathology. J Gastrointest Oncol 2012; **3**:251–261.

4 Monograph of the incidence of Gastric carcinoma in Middle East: Middle East Cancer Consortium (MECC). Available at: *http://seer.cancer.gov/publications/mecc/http://www.cancer.gov/cancertopics/pdq/treatment/gastric/HealthProfessional/page4#Reference4.1*. [accessed on 2014 Jan 10].

5 David Cunningham MD, William H. Allum: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer (MAGIC trial). N Engl J Med 2006; **355**:11–20.

6 Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, *et al.* ToGA Trial Investigators Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010; **376**:687–697.

7 Wang G, Huang H, Gao J, Chen P, You W, Wu B, Wang M. Tissue microarray analysis of topoisomerase IIalpha protein in gastric adenocarcinomas: histogenetic and prognostic implications. Cancer Genomics Proteomics 2011; **8**:127–134.

8 Gordon MA, Gundacker HM, Benedetti J, Macdonald JS, Baranda JC, Levin WJ, *et al.* Assessment of HER2 gene amplification in adenocarcinomas of the stomach or gastroesophageal junction in the INT-0116/SWOG9008 clinical trial. Ann Oncol 2013; **24**:1754–1761.

9 Bang Y, Chung H, Xu J, Lordick F, *et al.* Pathological features of advanced gastric cancer (GC): relationship to human epidermal growth factor receptor 2 (HER2) positivity in the global screening program of the ToGA trial. J Clin Oncol 2009; 27:15s. Abstract 4556.

10 Peleteiro B, Lunet N. Role of genetic and environmental risk factors in gastric carcinogenesis pathway, gastritis and gastric cancer — new insights in gastroprotection, diagnosis and treatments Paola Tonino (ed.) 2011.

11 Su X, Zhan P, Gavine PR, Morgan S, Womack C, Ni X, *et al.* FGFR2 amplification has prognostic significance in gastric cancer: results from a large international multicentre study. Br J Cancer 2014; **110**:967-975.