The role of human epidermal growth factor receptor (her2/neu) in the prognosis of gastric cancer: a review article

Sarah Ayad Abed*, Huda Abbas Kalaf*, Suhair Ayad Abed*
*College of Medicine/ University of Al-Qadisiyah/ Adiwaniyah Province/ Iraq
Emails of corresponding authors:
huda_ak87@yahoo.com, iraq93771@gmail.com

Abstract
Background: It is worth to mention that the ToGA trial published article described a relatively longer median survival for patients with positive expression of her2/neu in comparison with the overall trend of patients with such malignant tumor questioning the possibility of good prognostic implication of her2/neu gene amplification in association with gastro-esophageal junction tumors. This opinion is indeed in contrast to the observations of other authors who concluded that gene amplification and protein overexpression is associated with poor prognostic implication.
Aim of the study: The lack of consensus in available medical literatures concerning the role of her2/neu overexpression in association with gastric cancer justified the conduction and planning of the current study aiming at inferring a more clear judgment about such role.
Materials and methods: A search in the Google internet search engine was made using the key words gastric cancer and her2/neu. Any relevant medical publication containing these key words was considered seriously and studied thoroughly. The study was aiming at inclusion of researches with statistically adequate sample size and those which were published during the last three to four decades. Inclusion criteria included those articles that evaluated her2/neu overexpression by genetic or immune histochmeistry techniques and those containing an association between her2/neu overexpression and prognosis of gastric cancer measured directly be survival rate or indirectly by other prognostic markers such as grade of the disease, stage of the disease, lymphatic and or gastric invasion and distant metastasis.
Results: The studies that fulfilled the inclusion criteria were 11 studies and out of them, 3 studies mentioned no significant role for her2/neu, whereas, 8 of them were on the contrary. Therefore, most of previous studies, 8 out of 11 (72.7 %), provided insight to the poor prognostic association between her/2neu protein expression and gene amplification and gastric cancer.
Conclusion: The role of her/2neu protein expression and gene amplification in gastric cancer appears to be significant in predicting poor prognosis because of their association in the majority of previous studies with poor survival and or with indirect poor prognostic characteristics.
Key words: her2/neu, prognosis, gastric, cancer

Introduction

One of very well known and established practice in medical literatures is the role of the growth factor receptor (her2/neu) in the prognosis, as well as, the therapeutic targeting of various forms of breast cancer (1-4). However, a number of reports documented such role for this oncogene and its transcriptional product oncoprtein in the prognosis and in therapeutic targeting of gastric cancer (5-9). In breast cancer, the positive expression of her2/neu is aasociated with poor prognosis and this medical statement is sol solid in medical literature that can be considered a fact throughout the last three decades; however, this poor prognostic implication for her2/neu in breast cancer is not the same when applied in gastric cancer sicne

there is till now no clear consensus about its prognostic implication with this regard, in spite of the early opinion claiming a poor prognostic role in gastric cancer in line with its behavior in breast cancer (5).

From genetic point of view the gene locus for her2/neu is located on chromosome 17 and it is regarded as an proto-oncogene. The protein product of this gene is a member of HER-family and it is a "tyrosin kinase receptor protein" of about 185 kD (10-12). A number of malignant tumors in humans have been shown to be associated with overexpression and gene amplification of her2/neu (5, 13, 14). One of earliest reports about the poor prognostic association between breast malignancy and her2/neu was issued by Slamon *et al* in 1987 (15). Later on data from almost all research publications with this regard confirmed the poor prognostic implication of this tumor marker with malignant breast lesions (5, 13).

The picture concerning the association between prognosis of gastric cancer and the protein over-expression and gene amplification of her2/neu is still vague and needs further research work in order a clear consensus (5). One the most important medical publication dealing with prognostic implication of her2/neu gene amplification and protein over expression in association with gastro-esophageal junction malignant tumors is the "ToGA trial" (16). In 2012, Jørgensen and Hersom published a systemic analysis about the role of her/neu in gastric cancer with more update knowledge background (5). In the ToGA trial patients with malignant gastric tumors were randomly allocated into two groups, one receiving standard protocol of chemotherapy and the other receiving the combined trastuzumab and chemotherapy approach and the results were longer median survival in association with combined treatment (16). It is worth to mention that the ToGA trial published article described a relatively longer median survival for patients with positive expression of her2/neu in comparison with the overall trend of patients with such malignant tumor questioning the possibility of good prognostic implication of her2/neu gene amplification in association with gastro-esophageal junction tumors (16). This opinion is indeed in contrast to the observations of other authors who concluded that gene amplification and protein overexpression is associated with poor prognostic implication (5).

The lack of consensus in available medical literatures concerning the role of her2/neu overexpression in association with gastric cancer justified the conduction and planning of the current study aiming at inferring a more clear judgment about such role.

Materials and methods

A search in the Google internet search engine was made using the key words gastric cancer and her2/neu. Any relevant medical publication containing these key words was considered seriously and studied thoroughly. The study was aiming at inclusion of researches with statistically adequate sample size and those which were published during the last three to four decades. Inclusion criteria included those articles that evaluated her2/neu overexpression by genetic or immune histochmeistry techniques and those containing an association between her2/neu overexpression and prognosis of gastric cancer measured directly be survival rate or indirectly by other prognostic markers such as grade of the disease, stage of the disease, lymphatic and or gastric invasion and distant metastasis.

The study was carried out at the laboratory of Biology in the department of Anatomy and Biology at the College of Medicine/ University of Al-Qadisiyah at Adiwaniyah Province/ Iraq. Statistical analysis of included data was based on SPSS version 16 and Microsoft Office Excel 2007. Qualitative variables were presented in the form of count and proportions, whereas,

quantitative data were presented in the form of mean, range and standard deviations. The level of significance was set at $p \leq 0.05$.

Results

Summary of studies discussing the link between prognosis of gastric cancer and her2/neu over expression and gene amplification is shown in table 1. We tried our best included as many countries as possible to exclude the effect of ethnic variation on the results of the current study. Therefore, studies from Japan, Korea, China, Spain, United Kingdome, Thailand, Germany, Mexico and USA were included. In the study of Yonemura *et al*., in 1991 in Japan, 260 cases were included and the technique was Immunohistochemistry and a positive poor prognostic role was described between her2/neu expression and gastric cancer (17).

In the study of Mizutani *et al*., in 1993 in Japan, 226 cases were included and the technique was Immunohistochemistry and Southern blot hybridization and a positive poor prognostic role was described between her2/neu expression and gastric cancer (18). In the study of Kim *et al*., in 1994 in Korea, 152 cases were included and the technique was Immunohistochemistry and no prognostic role was described between her2/neu expression and gastric cancer (19). In the study of Chariyalertsak *et al*., in 1994 in Thailand, 309 cases were included and the technique was Immunohistochemistry and ELISA and a positive poor prognostic role was described between her2/neu expression and gastric cancer (20).

In the study of Webb *et al*., in 1996 in United Kingdome, 160 cases were included and the technique was Immunohistochemistry and ELISA and a positive poor prognostic role

was described between her2/neu expression and gastric cancer (21). In the study of Sanz-Ortega *et al*., in 2000 in Spain, 143 cases were included and the technique was Immunohistochemistry and a positive poor prognostic role was described between her2/neu expression and gastric cancer (22).

In the study of Allgayer *et al*., in 2000 in Germany, 189 cases were included and the technique was Immunohistochemistry and a positive poor prognostic role was described between her2/neu expression and gastric cancer (23). In the study of Pinto-de-Sousa *et al*., in 2002 in Portugal, 157 cases were included and the technique was Immunohistochemistry and a positive poor prognostic role was described between her2/neu expression and gastric cancer (24).

In the study of Yu *et al*., in 2009 in China, 1143 cases were included and the technique was Immunohistochemistry microarrays and a positive poor prognostic role was described between her2/neu expression and gastric cancer (25). In the study of Kunz *et al*., in 2011 in USA, 169 cases were included and the technique was Immunohistochemistry microarrays and no prognostic role was described between her2/neu expression and gastric cancer (26). In the study of Alvarado-Cabrero *et al*., in 2017 in Mexico, 93 cases were included and the technique was Immunohistochemistry and no prognostic role was described between her2/neu expression and gastric cancer (26).

Therefore, most of previous studies, 8 out of 11 (72.7 %), provided insight to the poor prognostic association between her/2neu protein expression and gene amplification and gastric cancer.

Table 1: Summary of studies discussing the link between prognosis of gastric cancer and her2/neu over expression and gene amplification

Reference	Authors/year	Country of study	Sample size	prognostic implication of her2/neu	Type of laboratory technique
17	Yonemura *et al*., 1991	Japan	260	Positive association (poor)	Immunohistochemistry
18	Mizutani *et al*., 1993	Japan	226	Positive association (poor)	Immunohistochemistry and Southern blot hybridization
19	Kim et al., 1994	Korea	152	No association	Immunohistochemistry
20	Chariyalertsak *et al*., 1994	Thailand	309	Positive association (poor)	Immunohistochemistry and ELISA
21	Webb *et al*., 1996	United Kingdome	160	Positive association (poor)	Immunohistochemistry and ELISA
22	Sanz-Ortega *et al*., 2000	Spain	143	Positive association (poor)	Immunohistochemistry
23	Allgayer *et al*., 2000	Germany	189	Positive association (poor)	Immunohistochemistry
24	Pinto-de-Sousa *et al*., 2002	Portugal	157	Positive association (poor)	Immunohistochemistry
25	Yu *et al*., 2009	China	1143	Positive association (poor)	Immunohistochemistry microarrays
26	Kunz *et al*., 2011	USA	169	No association	Immunohistochemistry microarrays
27	Alvarado-Cabrero *et al*., 2017	Mexico	93	No association	Immunohistochemistry

Discussion

Prognosis of malignant tumors is an essential characteristic in every day clinical and surgical practice, because both patients and health care providers aim at improving quality of life and survival in those who suffer these lethal medical conditions (28, 29). The role of immunohistochemistry and molecular techniques becomes increasingly vital with identifying certain biological molecules that could provide anticipatory potential to health care providers with respect to a variety of medical conditions and on the top of the list os these conditions, malignant tumors takes the lead (30). Tumor markers that are amenable for tissue identification play an important role in the daily work of medical laboratories. Among these her2/neu is very well known for its poor prognostic role in breast cancer.

Nevertheless, the types and tissues associated with other malignant tumors other than breast becomes increasingly analyzed in term of prognosis in association with this well known molecular proto-oncogen (5, 30). Gastric cancer is among common malignant tumors encountered all over the globe and in particular in certain Asian countries such as Japan, Korea and Chian (5). The association between her2/neu and gastric cancer has been evaluated by a number of previous authors (5, 17-27). However, a consensus, about its exact role still needs further research work. In the current review article, we tried to collect available information about such an association in published articles all over the world.

In the current study, most previously published articles favors the existence of poor

prognostic implication for her2/neu protein over expression and gene amplification in association with gastric malignant tumors.

Conclusion

The role of her/2neu protein expression and gene amplification in gastric cancer appears to be significant in predicting poor prognosis because of their association in the majority of previous studies with poor survival and or with indirect poor prognostic characteristics.

Acknowledgement

References

1 Pernas S, Tolaney SM. HER2-positive breast cancer: new therapeutic frontiers and overcoming resistance. *Ther Adv Med Oncol*. 2019;11:1758835919833519. Published 2019 Mar 19. doi:10.1177/1758835919833519

2 Mitri Z, Constantine T, O'Regan R. The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances in Therapy. *Chemother Res Pract*. 2012;2012:743193. doi:10.1155/2012/743193

3 Iqbal N, Iqbal N. Human Epidermal Growth Factor Receptor 2 (HER2) in Cancers: Overexpression and Therapeutic Implications. *Mol Biol Int*. 2014;2014:852748. doi:10.1155/2014/852748

4 Ishikawa T, Ichikawa Y, Shimizu D, et al. The role of HER-2 in Breast Cancer. *J Surg Sci*. 2014;2(1):4-9.

5 Jørgensen JT, Hersom M. HER2 as a Prognostic Marker in Gastric Cancer - A Systematic Analysis of Data from the Literature. *J Cancer*. 2012;3:137-144. doi:10.7150/jca.4090

6 Abrahao-Machado LF, Scapulatempo-Neto C. HER2 testing in gastric cancer: An update. *World J Gastroenterol*. 2016;22(19):4619-4625. doi:10.3748/wjg.v22.i19.4619

7 Boku N. HER2-positive gastric cancer. *Gastric Cancer*. 2014;17(1):1-12. doi:10.1007/s10120-013-0252-z

8 de Mello RA, Marques AM, Araújo A. HER2 therapies and gastric cancer: a step forward. *World J Gastroenterol*. 2013;19(37):6165-6169. doi:10.3748/wjg.v19.i37.6165

9 Cetin B, Ozet A. *HER2/neu* as target in gastric adenocarcinoma. *Transl Gastroenterol Hepatol*. 2016;1:59. Published 2016 Jul 22. doi:10.21037/tgh.2016.06.08

10 Telugu RB, Chowhan AK, Rukmangadha N, et al. Human epidermal growth factor receptor 2/neu protein expression in meningiomas: An immunohistochemical study. *J Neurosci Rural Pract*. 2016;7(4):526-531. doi:10.4103/0976-3147.188640

11 Fritz P, Cabrera CM, Dippon J, Gerteis A, Simon W, Aulitzky WE, et al. c-erbB2 and topoisomerase IIalpha protein expression independently predict poor survival in primary human breast cancer: A retrospective study. *Breast Cancer Res.* 2005;7:R374–84.

12 Moelans CB, van Diest PJ, Milne AN, Offerhaus GJ. Her-2/neu testing and therapy in gastroesophageal adenocarcinoma. *Patholog Res Int*. 2010;2011:674182. Published 2010 Dec 6. doi:10.4061/2011/674182

13 Ross JS, Slodkowska EA, Symmans WF. et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist.* 2009;14:320–368. .

14 Jørgensen JT. Targeted HER2 treatment in advanced gastric cancer. *Oncology.* 2010;78:26–33.

15 Slamon DJ, Clark GM, Wong SG. et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987;235:177–182.

16 Bang YJ, Van Cutsem E, Feyereislova A. et al. 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.

17 Yonemura Y, Ninomiya I, Yamaguchi A. et al. Evaluation of immunoreactivity for erbB-2 protein as a marker of poor short term prognosis in gastric cancer. *Cancer Res.* 1991;51:1034–1038.

18 Mizutani T, Onda M, Tokunaga A. et al. Relationship of C-erbB-2 protein expression and gene amplification to invasion and metastasis in human gastric cancer. *Cancer.* 1993;72:2083–2088.

19 Kim JP, Oh ST, Hwang TS, Chi JG. The prognostic significance of c-erbB-2 and p53 protein expressions in gastric carcinoma--a multivariate analysis of prognostic factors. *J Korean Med Sci.* 1994;9:248–253.

20 Chariyalertsak S, Sugano K, Ohkura H, Mori Y. Comparison of c-erbB-2 oncoprotein expression in tissue and serum of patients with stomach cancer. *Tumour Biol.* 1994;15:294–303.

21 Webb A, Scott-Mackie P, Cunningham D. et al. The prognostic value of serum and immunohistochemical tumour markers in advanced gastric cancer. *Eur J Cancer.* 1996;32A:63–68.

22 Sanz-Ortega J, Steinberg SM, Moro E. et al. Comparative study of tumor angiogenesis and immunohistochemistry for p53, c-ErbB2, c-myc and EGFr as prognostic factors in gastric cancer. *Histol Histopathol.* 2000;15:455–462.

23 Allgayer H, Babic R, Gruetzner KU. et al. c-erbB-2 is of independent prognostic relevance in gastric cancer and is associated with the expression of tumor-associated protease systems. *J Clin Oncol.* 2000;18:2201–2209.

24 Pinto-de-Sousa J, David L, Almeida R. et al. c-erb B-2 expression is associated with tumor location and venous invasion and influences survival of patients with gastric carcinoma. *Int J Surg Pathol.* 2002;10:247–256.

25 Yu GZ, Chen Y, Wang JJ. Overexpression of Grb2/HER2 signaling in Chinese gastric cancer: their relationship with clinicopathological parameters and prognostic significance. *J Cancer Res Clin Oncol.* 2009;135:1331–1339.

26 Kunz PL, Mojtahed A, Fisher GA. et al. HER2 Expression in Gastric and Gastroesophageal Junction Adenocarcinoma in a US Population: Clinicopathologic Analysis With Proposed Approach to HER2 Assessment. *Appl Immunohistochem Mol Morphol.* 2012 Jan;20(1):13–24.

.

27 Alvarado-Cabrero I, Gil-Hernández S, Ruelas-Perea A, Villaverde-Rodríguez D, Montes-Ochoa JR, Medrano-Guzmán R. Evaluación por inmunohistoquímica de la expresión del HER2 en cáncer gástrico. Estudio clínico-patológico de 93 casos [Immunohistochemical assessment of HER2 expression in gastric cancer. A clinicopathologic study of 93 cases]. Cir Cir. 2017 Nov-Dec;85(6):504-509. Spanish. doi: 10.1016/j.circir.2016.11.016. Epub 2017 Jan 6. PMID: 28069112.

28 Hui D. Prognostication of Survival in Patients With Advanced Cancer: Predicting the Unpredictable?. *Cancer Control.* 2015;22(4):489-497. doi:10.1177/107327481502200415

29 Mariotto AB, Noone AM, Howlader N, et al. Cancer survival: an overview of measures, uses, and interpretation [published correction appears in J Natl Cancer Inst Monogr. 2015 May;2015(51):97]. *J Natl Cancer Inst Monogr.* 2014;2014(49):145-186. doi:10.1093/jncimonographs/lgu024

30 Wesoła M, Jeleń M. A Comparison of IHC and FISH Cytogenetic Methods in the Evaluation of HER2 Status in Breast Cancer. Adv Clin Exp Med. 2015 Sep-Oct;24(5):899-903. doi: 10.17219/acem/27923. PMID: 26768643