LIBYAN JOURNAL OF MEDICINE
2019, VOL. 14, 1574532
https://doi.org/10.1080/19932820.2019.1574532

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Prevalence of Her3 in gastric cancer and its association with molecular prognostic markers: a Saudi cohort based study

Ayesha Ahmed

Department of Pathology, College of Medicine, Imam Abdulrahman Bin Faisal University and King Fahd Hospital of the University, Al-Khobar, Kingdom of Saudi Arabia

ABSTRACT

Her 3 is a member of epidermal growth factor receptors. Mutated, oncogenic Her3 is reported in gastric and colonic cancers with emerging evidence that Her3 can be a potential target for molecular therapies. There is a paucity of studies regarding Her3 and its prognostic implications in gastric cancer in our region. In this study, we evaluated prevalence of Her3 in gastric cancer, in a Saudi cohort of cases, along with its association with prognostic markers p53 and Ki-67. The study was conducted in Department of Pathology of King Fahd Hospital of Imam Abdulrahman Bin Faisal University, Dammam, KSA. Fifty cases of gastric carcinoma were selected from the pathology files that fulfilled the inclusion criteria. Clinico-pathological parameters, Laurens histological classification, and immunohistochemical staining for Her3, p53, and Ki-67 were done. Her 3 positive cases were also evaluated for Her-2neu co-expression. Her3 positivity was seen in 16% ($n = 8$) out of a total of 50 cases. The median age of presentation was 44 years. Within Her3 positive cases, a female preponderance of 63% ($n = 5$), presence of high grade tumors in 75% ($n = 6$), diffuse gastric carcinoma in 63% ($n = 5$), diffuse to focal p53 positivity in 63% ($n = 5$), and a high to moderate Ki-67 proliferation index in 75% ($n = 6$) of cases was seen. Her3 expression was independent of Her-2neu status. Her3 prevalence of 16% with a median age of 44 years at presentation was less than in other reported studies, highlighting the concept of ethnic and regional variation in tumor characteristics. Her3 association with diffuse gastric carcinoma, high grade tumors, diffuse to focal p53 positivity and high to moderate Ki-67 proliferation index points towards a more aggressive clinical behavior.

ARTICLE HISTORY
Received 10 June 2018
Accepted 16 January 2019

KEYWORDS
Her3; gastric cancer; prevalence; prognosis; molecular markers

1. Introduction

The Her/ErbB family of receptors, EGFR, Her2-neu, Her3, and Her4 are involved in multiple, inter related, complex, and tightly regulated signal transduction pathways that culminate in cellular adhesion, proliferation, migration, and angiogenesis. These receptors exhibit three domains: an extracellular, glycosylated domain for ligand attachment, a transmembrane domain, and an intracytoplasmic domain with tyrosine kinase activity. Ligand binding initiates receptor's homo or hetero-dimerization with resultant activation of tyrosine kinase that triggers signaling pathways [1]. Aberrant signaling in 'Her' pathways can lead to development of multiple solid malignancies [2].

The functions of Her3 in carcinogenesis are always ignored as compared to EGFR and Her2-neu [3,4]. Her3 lacks an intrinsic tyrosine kinase activity so it hetero-dimerizes with Her2-neu, an orphan receptor with no known ligand [5]. This mutual need based hetero-dimerization leads to direct binding of p85 subunit of PI3K, which is the regulatory subunit of PI3K. Her3 contains six p85-binding motifs whereas Her2 cannot directly bind and activate p85. PI3K activation triggers PI3K/AKT signaling pathway that plays an important role in tumorigenesis. The importance of this bi-receptor unification is highlighted by their co-expression in breast cancer and breast cancer derived cell lines. The symbiotic relationship of these two receptors is pivotal for maintenance of cell viability in Her2-neu breast cancer cells and in Her2-neu mediated carcinogenesis. Therapeutically, this has been exploited as Her2-neu inhibition using tyrosine kinase inhibitors or anti Her2-neu antibody pertuzumab suppresses the dimerization and Her3-mediated downstream activation of PI3K signaling in Her2-neu overexpressing cells [6].

Mutated oncogenic Her3 has been reported in various malignancies, including gastric, colorectal, breast, ovarian, pancreatic, prostatic, bladder, lung, squamous cell carcinoma, and melanoma. Her3 overexpression may be associated with poor prognosis and unfavorable survival mediated by PI3K/AKT signaling pathway [7]. Her3 has a therapeutic role too and there is emerging evidence that Her3 can be a potential target for molecular therapies [8]. AntiHer3 antibodies used in conjunction with anti-estrogen treatment in breast cancer can

CONTACT Ayesha Ahmed aahmed@iau.edu.sa Department of Pathology, College of Medicine, Imam Abdulrahman Bin Faisal University and King Fahd Hospital of the University, Al-Khobar, Kingdom of Saudi Arabia

result in diminished tumor cell growth and delayed resistance [6]. In gastric cancer, a large amount of direct evidence has emerged regarding the benefit of anti-HER 3 agents in combination with EGFR tyrosine kinase inhibitors, as well as anti-HER2 agents [7].

Her3 expression pattern in gastric carcinoma with its associated poor patients prognostics and survival has not been extensively investigated in our region where there is paucity of such studies. The previous studies mainly highlight the association of Her3 overexpression with poor patient's prognosis and survival mediated by PI3K/AKT signaling pathway. In this study, we attempted to investigate if p53 signaling pathway has an association with Her3 expressivity pattern and poor patients prognostics. In this regard, we evaluated Her3 expression by immunocytochemical analysis and its association with prognostic markers p53 and Ki-67 and clinico-pathological parameters in a set of GC cases from a Saudi cohort of patients.

2. Material and methods

This study was conducted out in the Department of Pathology of King Fahd Hospital of Imam Abdulrahman Bin Faisal University, Dammam, KSA, after approval by the Institutional Review Board of the University.

In this descriptive (cross sectional) study, 50 cases of GC that comprised endoscopic biopsies and gastric resection specimens were selected from the pathology files that fulfilled the inclusion criteria. The study was carried out in the period of 2015-2017. The cases were selected in the time interval spanning over 10 years before the study period. Initially, a sample size of 45 was calculated for a population size of 10,000 patients (cases) registered in hospital system. A confidence level of 95% was taken into consideration. The margin of error was 5% and response rate was of 3%. These statistics were based on cancer incidence report 2010 for GC in Saudi Arabia [9]. However, as 50 cases were found that fulfilled the inclusion criteria so the final number of cases used in the study were 50.

The inclusion criteria consisted of presence of necessary patient's information in the hospital computerized medical records and availability of paraffin tissue blocks with sufficient tissue specimen. The tissue specimen available was calibrated as sufficient if enough tissue material was present to carry out the routine histopathological and immunohistochemical workup.

Parafin blocks were sectioned into 4 µm thickness and stained for routine hematoxylin and eosin Immunostaining for Her3, p53, and Ki-67 was then done utilizing 3,3′-diaminobenzidine (DAB) as a chromagen and employing the labeled streptavidin-biotin (LSAB) methodology. Prediluted antibodies for Her3, Ki-67and p53 using clones DAKH31C2, MIB-1, and DO-7, respectively were used in an automated Ventana immunostainer. Her 3 positive cases were also stained for Her2-neu using Her-2 neu clone CB11 and utilizing the same procedure.

The routine hematoxylin and eosin and immunostained slides were evaluated and analyzed by light microscopy by the pathologist AA. GC was classified histologically into **diffuse** and **intestinal** type as delineated in Laurens classification [10]. Interpretation for Her3, Her2-neu, p53, and Ki-67 were carried out as follows:

2.1. Her3 interpretational guidelines

Membranous and or cytoplasmic immunostaining was considered as positive. The staining pattern and intensity was attributed the following scores [11]:

Score 0: Complete absence of staining.

Score 1: Faint or barely perceptible partial staining in 10% of tumor cells

Score 2: Weak to moderate complete/incomplete membranous or cytoplasmic staining seen in 10% of tumor cells

Score 3: Strong intense complete membranous or cytoplasmic staining in 10% of tumor cells.

The scores were calibrated as positive and negative as follows:

Negative: Score 0 and 1

Positive: Scores 2 and 3.

In gastric resection specimens staining present in atleast 10% of the tumor cells (as stated above), whereas in endoscopic biopsies staining seen in atleast a group of five tumor cells was considered for evaluation and scoring.

2.2. Her-2 neu interpretational guidelines

The same scoring guidelines were employed for Her2-neu as for Her3. However, only membranous staining was considered as positive [11].

2.3. p53 interpretational guidelines

Nuclear staining was considered as positive p53 mutation status. Cytoplasmic positivity was not taken into account. The results were calibrated as follows [12]:

Negative: No staining or staining seen in less than 10% of tumor cell nuclei.

Focally positive: Unequivocal staining present in 10–50% of tumor cell nuclei.

Diffusely positive: Unequivocal staining present in more than 50% of tumor cell nuclei.

2.4. Ki-67 interpretational guidelines

Nuclear staining was considered as positive Ki-67 proliferation index. Cytoplasmic positivity was not taken

into consideration. The results were calibrated as follows [13]:

Low proliferative activity: nuclear staining in less than 10% of tumor cell nuclei.

Moderate proliferative activity: nuclear staining in 10–40% of tumor cell nuclei.

High proliferative activity: nuclear staining in more than 40% of tumor cell nuclei.

Data was entered into SPSS (version 19). Frequencies (percentages) for expression of Her3, p53, and Ki-67 were calculated by using descriptive statistics. Frequency of p53 and Ki-67 was calculated for Her3 positive cases. This was then compared with frequency of p53and Ki-67 in Her3 negative cases. Chi square test was used for comparison. A p value of less than 0.05 was considered as statistically significant. The percentage of Her3 positive cases showing co-expression of Her2-neu was also calculated.

3. Results

A total of 50 cases (patients) of GC were evaluated. The patients had a median age of 67 years (minimum and maximum 42 and 88 years). Overall female to male ratio was 13:37. Intestinal type GC was seen in 27 (54%) and diffuse type GC was seen in 23 (46%) of cases. There were 43 (86%) biopsies and 7(14%) partial gastrectomy specimens.

Table 1 shows Her 3 prevalence pattern and Table 2 shows extent of p53 and Ki-67 within overall GC cases.

Out of the total Her3 positive cases (n = 8), diffuse type GC was seen in 63% (n = 5) (Figure 1(a–b)) and intestinal type in 37% (n = 3). High grade tumors were 75% (n = 6) and low grade (moderately differentiated) were 25% (n = 2). No well differentiated tumor was identified (Table 3).

Her3 positivity (Figure 1(c–d)) was seen mostly in females, 63% (n = 5) as compared to males, 37% (n = 3). The median age of overall Her 3 positive GC cases was 44 years and mean age was 48.75(SD 24.04). The cases showing 3+ positivity were seen in a younger age group at a mean age of 43 years (SD 3.75). One of the cases was also seen at 36 years of age. There were two cases of 2+ Her3 positivity, each

Table 1. Her3 prevalence pattern in gastric carcinoma (n = 50).

Her-3 status	Her-3 expression pattern	N (total 50)	% Age	Overall percentage
Negative	**0**	40	80*	84% (n = 42)
	1+	2	4	
Positive	**2+**	2	4	16% (n = 8)
	3+	6	12	

*A p value of <0.01 determined by chi square test.

Table 2. p53 and Ki-67 in gastric carcinoma (n = 50).

p-53	Diffuse	18% (n = 9)
	Focal	54% (n = 27)
	Negative	28% (n = 14)
Ki-67	High	40% (n = 20)
	Moderate	30% (n = 15)
	Low	30% (n = 15)

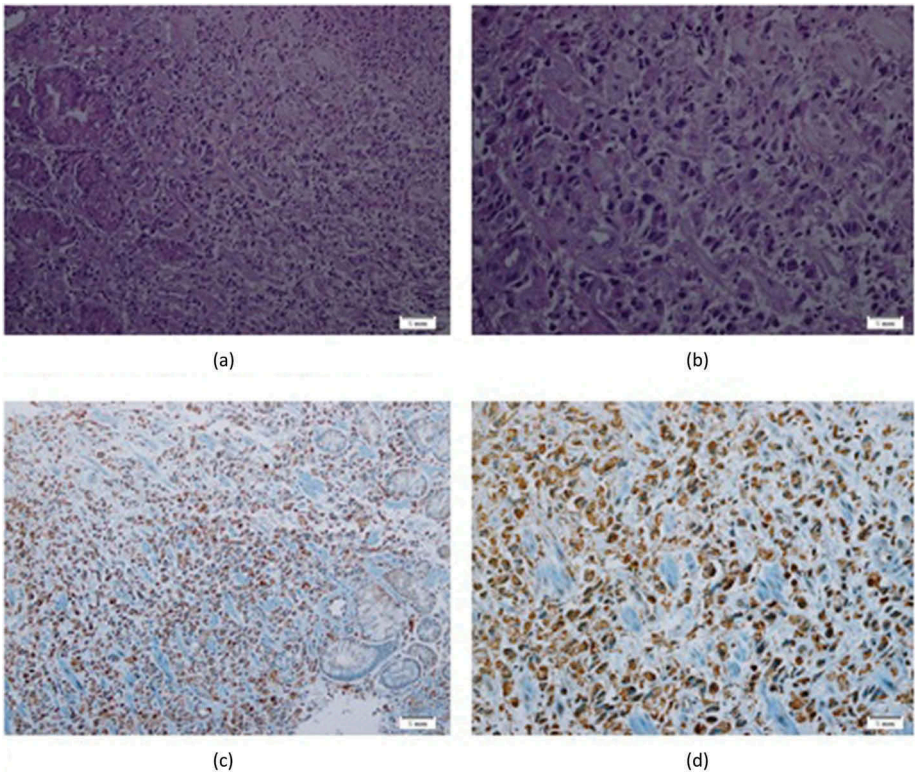

Figure 1. (a) Diffuse gastric carcinoma, H&E stain x20. (b) Diffuse gastric carcinoma, H&E stain x40. (c) 3+ Her3 positivity in diffuse gastric carcinoma, IHC, x20. (d) 3+ Her3 Positivity in diffuse gastric carcinoma, IHC, x40.

Table 3. Her3 positive cases with clinicopathological parameters (n = 8).

Her3 status (n = 8)	Gender	Age	Specimen type	Tumor type	Tumor grade Low grade (well to moderate) vs. High grade (poorly) differentiated
3+	M	36	Biopsy	Intestinal	Low grade (moderate)
3+	M	43	Biopsy	Intestinal	Low grade (moderate)
3+	M	45	Biopsy	Intestinal	High grade
3+	F	44	Biopsy	Diffuse	High grade
3+	F	44	Biopsy	Diffuse	High grade
3+	F	46	Biopsy	Diffuse	High grade
2+	F	62	Biopsy	Diffuse	High grade
2+	F	70	Biopsy	Diffuse	High grade

presenting at ages of 62 and 70 years, respectively (Table 3).

Table 4 presents the relationship of Ki-67 proliferation index with Her3 positive and negative expression pattern.

Her3 positive cases revealed an overall moderate to high Ki-67 proliferation index in 75% (n = 6) of cases and a low index in 25% (n = 2) of cases (Table 4).

There was no relationship between low, moderate, or high Ki-67 proliferation index and Her3 positive or negative expression pattern (Table 4).

Table 5 presents the relationship of p53 with Her3 positive and negative expression pattern.

Her 3 positive cases revealed an overall 63% (n = 5) of p53 positivity with diffuse p53 present in 37.5% (n = 3) and focal in 25% (n = 2) of cases (Table 5).

Diffuse p53 positivity was present in 37.5% (n = 3) of Her3 positive cases in comparison to 14.28% (n = 6) of Her3 negative cases (Diffuse *p-53 positivity was significantly high, p value <0.01 in cases with Her3 positivity)* (Table 5).

Table 4. Ki-67 in Her3 positive and negative cases in gastric carcinoma (n = 50).

Her3 expression pattern		Ki-67 High	Ki-67 Mod	Ki-67 Low
Positive (n = 8)	**Total (n = 8)**	3 (37.5%)	3 (37.5%)	2 (25%)
	2+ (n = 2)	1	1	0
	3+ (n = 6)	2	2	2
Negative (n = 42)	**Total (n = 42)**	17 (40.47%)	12 (28.57%)	13 (30.95)
	1+ (n = 2)	1	1	0
	0 (n = 40)	16	11	13

Table 5. p53 in Her3 positive and negative cases in gastric carcinoma (n = 50).

Her3 expression pattern		p-53 Diffuse	p-53 Negative	p-53 Focal
Positive (n = 8)	**Total (n = 8)**	3 (37.5%)*	3 (37.5%)	2 (25%)
	2+ (n = 2)	1	1	0
	3+ (n = 6)	2	2	2
Negative (n = 42)	**Total (n = 42)**	6 (14.28%)	11 (26.19%)	25 (59.52%)*
	1+ (n = 2)	0	2	0
	0 (n = 40)	6	9	25

*A p value of <0.01 determined by chi square test.

Focal p53 positivity was present in 59.25% (n = 25) of Her3 negative cases in comparison to 25% (n = 2) of Her3 positive cases. (Focal *p-53 positivity was significantly high, p value <0.01 in cases with Her3 negativity*) (Table 5).

Negative p53 had no relationship with Her3 positive or negative expression pattern (Table 5).

No co-expression of Her3 with Her-2neu-was observed.

4. Discussion

Her/ErbB or Human epidermal growth factor receptors EGFR, Her2-neu, Her3, and Her4 play an important role in gastric carcinogenesis and patients prognosis. A lot of attention has been attributed to Her2-neu. Her3 role as a predictive factor in GC has been documented in a very few studies. A meta-analysis by Cao et al. [3] highlighted five studies that show strong association of Her3 overexpression with depth of tumor invasion, lympho-vascular invasion, lymph nodal metastasis, tumor recurrence, and a shortened overall patients 5 year survival time. Studies highlighting these associations and parameters with Her3 expression pattern in GC are almost non-existent in our region to the best of our knowledge.

Her3 prevalence pattern in GC shows a lot of variation. It was seen in 16% in our set of cases. Other studies have documented a much higher percentage. Hayashi et al. in a Japanese cohort of 134 patients with GC reported Her3 prevalence to be 59% [14]. Multiple Chinese studies reported a variable expression pattern like Wu et al. 84% [15], Tang et al. 62% [16], and He et al. 21% [17]. A wide range of expressivity pattern can thus be discerned. We have a low prevalence than reported in other studies, though it is somewhat at par with that documented by He at al. [17]. This low pattern of Her3 prevalence raises several issues that need to be discussed. Could this pattern of Her3 representation in our region be attributed to the concept of ethnic and geographic variations in cancer characteristics? Tumors in each region are known to have their own inherent distinct features. These variations epitomize development and monitoring of tailored therapeutic regimens depending on indigenous cancer demographics and characteristics. Such findings call for a more in depth analysis of tumor inherent features and statistics.

All of the cases in which there was Her3 positivity were biopsy specimens in our set of cases. Most gastric tumors are heterogeneous in their expression pattern of different proteins. The criterions employed for biopsy specimens in GC are just presence of an aggregate of five tumor cells whereas in resection specimen a 10% of tissue material is considered [11]. A small biopsy specimen, due to tumor heterogeneity,

has always a chance of missing on to the areas that could be more representative in protein expression. We had a total of 86% of biopsy specimens as compared to 14% of partial gastrectomies. Could there be a possibility that the areas with Her3 positivity could not be represented in the small biopsy specimen and hence a low prevalence was attained. Additionally different modes of staining, criterions for protein expression interpretations and employing specialized modalities like tissue microarray or fluorescence *in situ* hybridization (FISH) could also play a role in highlighting or downgrading the protein expression pattern. A large scale more extensive investigations need to be carried out to elaborate such complexities.

This expression pattern was mostly seen in females in other studies, 41% by Hayashi et al. [14], 44% by Wu et al. [15], 61% by Tang et al. [16], and 79% by He et al. [17]. A female preponderance was also seen in our cases with 63% of Her3 positive tumors being in females (n = 5). This is in concordance with other studies. Age distribution however showed a stark difference. An age range of 59–60 years was reported in other studies [14,17]. Her 3 positive tumors in our set of cases presented at a median age of 44 years and a mean age of 48.75(SD 24.04). The cases showing 3+ Her 3 positivity were seen in a younger age group at a mean age of 43 years (SD 3.75). One case was also seen at 36 years of age. The two cases with 2+ Her3 positivity, presented at ages of 62 and 70 years. There was hence an inverse relationship between Her 3 expression and age. An overall younger age of presentation of Her3 positive tumors and an increasing Her3 expression with decreasing age may have a profound clinical impact on the patients. Her3 tumors are considered to be more aggressive and its stronger expression in a younger age group in this regional cohort could imply a more aggressive cancer behavior and poor patient's prognostics in this region.

Additionally, this finding also suggests that a screening strategy for GC cases need to be started at a younger age in this region. According to Saudi Cancer Registry 2010, 300 new cases of GC are diagnosed yearly and this makes it the 9th most common cancer in Saudi Arabia [9]. There is yet no national screening program for GC and approximately 34% of GC cases present with metastasis and the remaining with a locally advanced disease [18].

Out of the total Her3 positive cases, 63% of the tumors were diffuse type and 37% intestinal type. Different studies have reported a different correlation of Her 3 expression with histological type of GC. Sanidas et al. in a series of 91 advanced GC reported no difference in Her3 expression between the two histological types [19]. Tang et al. reported Her3 overexpression to have a strong association with diffuse type GC in concordance with our study [16]. Her3 signaling pathway involves its phosphorylation that activates phosphoinositide-3-kinase (PI3 K)/Akt. This signal transmitting pathway leads to loss of cell to cell interaction that could contribute to development of a dedifferentiated, diffuse type GC, and also increase cell motility and invasion thus and promoting metastasis [20].

In all our cases of Her 3 positivity, none of these showed a simultaneous expression of Her2-neu. Her3 is known to lack intrinsic tyrosine kinase activity. To overcome this deficiency Her3 forms heterodimers with other members of 'Her' family. A combination with Her2 is considered to be the most preferred union which can activate the downstream signaling pathways most efficiently [20,21]. Her 2 has been extensively investigated whereas data on Her 3 in combination with Her3 is somewhat deficient. A study by Zhang et al. [11] evaluated simultaneous expression of Her3 and Her2-neu and they also reported lack of their co-expression. This finding does not substantiate the observation of Her3 exclusive dependency on Her2 for it signaling pathways. More studies need to be carried out to elucidate such controversies.

The role of gastric Her3 in patient's prognosis is yet debated and no definite consensus has been formulated. Seventy-five percent (n = 6) of our Her3 positive cases were high grade tumors. Jacome et al. [22] in a retrospective study comprising 201 patients with gastric and gastroesophageal adenocarcinoma reported absence of any correlation between Her3 cytoplasmic positivity, tumor depth, nodal metastases or TNM stage. Correlation with membranous positivity was not evaluated as only one patient had shown such a positive pattern. Hayashi et al. demonstrated Her3 positivity to be associated with a poor patient's prognostics and a decreased overall survival [14]. Ocana et al. in a meta-analysis comprising 12 studies, evaluated patients survival rate in relation to Her3 expression pattern in breast, gastric, and colorectal carcinoma. They concluded that Her3 expression and poor patient's outcome are directly related [23].

To understand prognostic implication of Her3 in gastric cancer, we evaluated its expressivity pattern with Ki-67 and p53. These markers have been established as indicative of prognosis in cancer in general. A moderate to high Ki-67 proliferation index was seen in 75% of our cases (Table 4). Ki-67 is a marker for cellular proliferation. Its role in gastric cancer is controversial with different studies attributing it a contrasting characteristic. It has been reported to be a good prognostic marker in early gastric carcinoma with well differentiated histology and not in advanced gastric carcinoma [24]. On the other hand its association with high grade tumors with an advanced stage and poor patient's prognostics has also been documented [13]. The tumors

in our study with Her 3 expression were predominantly high grade with 63% being diffuse type gastric carcinoma that are poorly differentiated aggressive tumors. Hence, Ki-67 in our study had a strong association with high grade tumors.

p53 protein is a tumor suppressor gene and its mutation is seen in more than 50% of tumors of various origins. Expression of p53 is considered as an independent prognostic marker and is associated with more aggressive tumor characteristics [25]. In our study cases with Her3 positive expression, p53 positivity was seen in 63% ($n = 5$), with diffuse p53 seen in 37.5% and focal seen in 25% of cases. Focal positivity was also seen in 59.52% of Her3 negative cases (Table 5). In a study by Yallowitz et al., in breast cancer, a strong relation between mutant p53 and EGFR family of receptors was documented and they considered p53 as a pivotal player and a possible target in Her1(EGFR) and Her2 ((ErbB2) positive breast cancer. They concluded that mutant p53 cooperates with Her1 and Her2-neu and leads to their signal amplification that culminates into mammary stem cell expansion and uncontrolled mammary cell proliferation [26]. A relationship between p53 and Her3 specifically has not been documented so far, but a shift from a significant focal expression in Her3 negative cases to a diffuse expression in Her3 positive cases, in our study could point towards such liaison and partnership in gastric carcinogenesis.

5. Conclusion

Her3 prevalence of 16% with and a median age 44 years of presentation was less than in other reported studies, highlighting concept of ethnic variation in tumor characteristics. Her3 association with diffuse gastric carcinoma, high grade tumors, diffuse to focal p53, and a moderate to high Ki-67 points towards a more aggressive clinical behavior pattern.

Her3 is yet aiming to be a potential target for molecular therapies. Her3 testing however, needs to become part of all gastric carcinoma diagnostic and therapeutic protocol. The treatment can then be tailored according to patient's individual tumor characteristics. This study unravels some indigenous geographical pattern and inherent immunohistochemical characteristics of Her3. However, more such studies with addition of molecular studies and extensive clinico-pathological correlations need to be conducted to pave a way for Her3 in contributing positively in improving patient's poor clinical outcome in GC.

Disclosure statement

No potential conflict of interest was reported by the author.

Funding

This work was supported by the Imam Abdulrahman Bin Faisal University (formerly University of Dammam) [2011011].

ORCID

Ayesha Ahmed http://orcid.org/0000-0002-2036-7067

References

[1] Sukawa Y, Yamamoto H, Nosho K, et al. HER2 expression and PI3K-Akt pathway alterations in gastric cancer. Digestion. 2014;89(1):12–17.
[2] Amann J, Kalyankrishna S, Massion PP, et al. Aberrant epidermal growth factor receptor signaling and enhanced sensitivity to EGFR inhibitors in lung cancer. Cancer Res. 2005 Jan 1;65(1):226–235.
[3] Cao GD, Chen K, Xiong MM, et al. HER3, but not HER4, plays an essential role in the clinicopathology and prognosis of gastric cancer: a meta-analysis. PloS one. 2016 Aug 18;11(8):e0161219.
[4] Berger MB, Mendrola JM, Lemmon MA. ErbB3/HER3 does not homodimerize upon neuregulin binding at the cell surface. FEBS Lett. 2004 Jul 2;569 (1–3):332–336.
[5] Le Wilks ST. Potential of overcoming resistance to HER2-targeted therapies through the PI3K/Akt/mTOR pathway. Breast. 2015 Oct;24(5):548–555.
[6] Mishra R, Patel H, Alanazi S, et al. HER3 signaling and targeted therapy in cancer. Oncol Rev. 2018 May 16; 12(1):355.
[7] Wang L, Yuan H, Li Y, et al. The role of HER3 in gastric cancer. Biomed Pharmacother. 2014 Jul;68(6):809–812.
[8] Jaiswal BS, Kljavin NM, Stawiski EW, et al. Oncogenic ERBB3 mutations in human cancers. Cancer Cell. 2013 May 13;23(5):603–617.
[9] Cancer Incidence Report Saudi Arabia, Kingdom of Saudi Arabia, Council of Health Services. Saudi cancer registry, April 2014. [cited 2018 Jun 4]. Available from: www.scr.org.sa
[10] Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.
[11] Zhang XL, Yang YS, Xu DP, et al. Comparative study on overexpression of HER2/neu and HER3 in gastric cancer. World J Surg. 2009 Oct;33(10):2112–2118.
[12] Busuttil RA, Zapparoli GV, Haupt S, et al. Role of p53 in the progression of gastric cancer. Oncotarget. 2014 Dec 15;5(23):12016–12026.
[13] Saricanbaz I, Karahacioglu E, Ekinci O, et al. Prognostic significance of expression of CD133 and Ki-67 in gastric cancer. Asian Pac J Cancer Prev. 2014; 15(19):8215–8219.
[14] Hayashi M, Inokuchi M, Takagi Y, et al. High expression of HER3 is associated with a decreased survival in gastric cancer. Clin Cancer Res. 2008 Dec 1;14(23):7843–7849.
[15] Wu X, Chen Y, Li G, et al. Her3 is associated with poor survival of gastric adenocarcinoma: her3 promotes proliferation,survival and migration of human gastric cancer mediated by PI3K/AKT signaling pathway. Med Oncol. 2014 Apr;31(4):903.

[16] Tang D, Liu CY, Shen D, et al. Assessment and prognostic analysis of EGFR, HER2, and HER3 protein expression in surgically resected gastric adenocarcinomas. Onco Targets Ther. 2014 Dec 16;8:7–14.
[17] He XX, Ding L, Lin Y, et al. Protein expression of HER2, 3, 4 in gastric cancer: correlation with clinical features and survival. J Clin Pathol. 2015;68:374–380.
[18] Alshomimi S, Alsaleem H. Comparing the treatment of gastric cancer between Korea and Saudi Arabia. Transl Gastroenterol Hepatol. 2017;2:32.
[19] Sanidas EE, Filipe MI, Linehan J, et al. Expression of the c-erbB-3 gene product in gastric cancer. Int J Cancer. 1993 Jul 30;54(6):935–940.
[20] Kobayashi M, Iwamatsu A, Shinohara-Kanda A, et al. Activation of ErbB3-PI3-kinase pathway is correlated with malignant phenotypes of adenocarcinomas. Oncogene. 2003 Mar 6;22(9):1294–1301.
[21] Srini Srinivasan R, Leverton KE, Sheldon H, et al. Intracellular expression of the truncated extracellular domain of c-erbB-3/HER3. Cell Signal. 2001 May;13 (5):321–330.
[22] Jácome AA, Wohnrath DR, Scapulatempo NC, et al. Prognostic value of epidermal growth factor receptors in gastric cancer: a survival analysis by Weibull model incorporating long-term survivors. Gastric Cancer. 2014 Jan;17(1):76–86.
[23] Ocana A, Vera-Badillo F, Seruga B, et al. HER3 overexpression and survival in solid tumors: a meta-analysis. J Natl Cancer Inst. 2013 Feb 20;105(4):266–273.
[24] Ko GH, Go SI, Lee WS, et al. Prognostic impact of Ki-67 in patients with gastric cancer-the importance of depth of invasion and histologic differentiation. Medicine (Baltimore). 2017 Jun;96(25):e7181.
[25] Al-Moundhri MS, Nirmala V, Al-Hadabi I, et al. The prognostic significance of p53, p27 kip1, p21, waf1, HER-2/neu, and Ki67 proteins expression in gastric cancer: a clinicopathological and immunohistochemical study of 121 Arab patients. J Surg Oncol. 2005 Sep 15;91(4):243–252.
[26] Yallowitz AR, Li D, Lobko A, et al. Mutant p53 amplifies epidermal growth factor receptor family signaling to promote mammary tumorigenesis. Mol Cancer Res. 2015 Apr;13(4):743–754.