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RESEARCH ARTICLE

GATA3 - IS IT A PROGNOSTIC MARKER IN BREAST CARCINOMA?"

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Abstract

GATA binding proteins are among the new prognostic factors being explored. My area of interest is GATA3 to correlate it with tumor size, nodal status ,tumor grade, Estrogen receptor, Progesterone receptor and HER2neu receptors in breast carcinoma patients This was a quantitative correlational study Patient were enrolled using consecutive non probability sampling method. GATA3 was inversely related with tumor size ,nodal status and grade. Estrogen positivity was associated with higher GATA3. However Progesterone and HER2Neu receptors statuses did not show any significant association with GATA3 levels. This study concludes that GATA3 expression can be used as a prognostic marker of breast cancer.

Introduction:-

Breast cancer is among the most common cancers worldwide.[1][2]According to a data from Asia in 2012, a total of 639,824 cases of breast cancer were recorded. Top five Asian countries included China, India, Japan, Indonesia and Pakistan. These five countries constituted 59.7% of total cases in Asia. [3]Deaths that occurred due to breast cancer were 228,926 of which top five contributing countries were India, China, Indonesia, Pakistan and Japan. According to this data Pakistan is among the top 5 countries having highest burden of disease.[3]

In Pakistan, Institute of Nuclear Medicine and Oncology (INMOL) collected data from January 2000 to December 2009. During this time 28,740 patients reported with cancer, among them 6718 patients had breast cancer, constituting 23% of the total cases reported. This shows huge burden of breast cancer in Pakistan.[4]Keeping in view such a high incidence and mortality of the disease, various dimensions of breast cancer needs to be explored in our country.[4]

Breast cancer prognosis depends on various factors which include tumor size, nodal status, lymphovascular invasion and histological grade. [5]Due to the vast diversity in the prognosis of the breast cancer patients, researchers are constantly exploring newer prognostic markers to guide for better prediction of the survival as well as deciding among various management options available.[5]GATA binding proteins are among the new prognostic factors being explored. [6][7]GATA binding proteins control the development of various tissues by activating or repressing transcription factors.[8] Therefore role of this family of genes in human cancers needs to be considered.[9]GATA family of transcription factors includes 6 transcription factors (GATA1-GATA6).[10] Among them GATA1 is found in all megakaryoblastic leukemias, GATA3 is associated with breast cancer, GATA4 and GATA5 is expressed in colorectal and lung cancer.[10]10 11 GATA binding protein 3 (GATA3) is located on chromosome 10 and it has been studied to predict prognosis and survival in patients with breast carcinoma in some studies.[8][11][12]

Due to its correlation with breast cancer my area of interest is GATA3. It is one of the six members of a family of zinc finger transcription factors. It attaches to the matched DNA sequence (A/T) GATA (A/G) and synchronizes cellular proliferation events and cell survival14 15 .GATA3 has been associated with good prognosis in breast [illegible] the data in previous [illegible] is a lot of gray area to [illegible] r size, tumor grade, lymphovascular invasion, Estrogen receptor, progesterone receptor and HER2neu receptors in breast carcinoma patients.

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Objective:-

To correlate GATA3 with tumor size, nodal status ,tumor grade, ,Estrogen receptor, progesterone receptor and HER2neu receptors in breast carcinoma patients.

Opertaional defination:
Tumor size
T0: no evidence of primary tumor
T1 :< 2cm
T2 : 2 to 5cm
T3 :> 5cm
T4: any size tumor with direct extension to chest wall or skin.

Tumor grade:
Grade1: looks most like normal breast cells and is usually slow-growing
Grade2: looks less like normal cells and is growing faster
Grade 3: looks different to normal breast cells and is usually fast-growing

Hormone receptor status:
It is Defined on the basis of the immuno-histochemical expression of Estrogen receptor (ER), human epidermal growth factor HER2-Neu and Progesterone receptor (PR) on biopsy specimen of breast cancer patients.

Material and Methods:-

This was a quantitative correlational study, conducted at Oncology department of Fauji Foundation Hospital Rawalpindi, from November 2018-november 2019 sample size is 50 patients based on parent's study population. Patient were enrolled using consecutive non probability sampling method.

a) Inclusion Criteria:
1. Patient aged 12 -75years
2. Histopathologic evidence of breast cancer
3. Chemo naive patients
4. Baseline echocardiography showing Ejection Fraction > 50 %
5. Normal blood counts, liver and kidney function tests.

b) Exclusion Criteria:
1. Patients who received previous Chemotherapy.
2. Pregnancy
3. Recurrent breast cancer
4. Concomitant other malignancy

Data was analyzed by SPSS version 23.0.The categorical variables like gender, tumor size , nodal status, histological grade ,GATA3 levels, ER, PR and HER 2neu were presented as frequency and percentages .The quantitative variables like age presented as mean and standard deviation. In analytical statistics qualitative variables like tumor size, nodal status, histological grade, ER, PR and HER2Neu statuses were associated with GATA3 levels using chi square-test and Pearson's correlation coefficients. Mean values of GATA3 levels were compared with mean values of ER,PR,HER2Nneu receptors with independent sample t test. A p-value of 0.05 was considered significant in all statistical analyses.

Results:-

The mean age of patients was 52.8±10.9 years in this study with a range of 41 to 60 year. Of the total 50 cases, the T3 (19, 38.0%) and T2(16, 32.0%) were most common T stage in our patients, while the most common nodal stage was N2 (17, 34.0%). Most tumors had histological tumor grade 3 (17 , 34.0%) followed by grade 1 in 15(30.0%) patients.

It was noted that tumor size at presentation was larger (T3 and T4) in patients with lower GATA3 levels whereas smaller tumor sizes (T1 and T2) were found in most of the patients with higher level of GATA3 (p-value of 0.008). Similarly, the nodal status was high (N2 and N3) in patients having low GATA3 level whereas it was found higher in patients having nodal status of N0 and N1 (p-value of 0.001). We also noted that tumor grade had a reverse relation with GATA3 level, the low levels being found in advanced tumor grades (grade 3 and grade 4) whereas higher levels being exhibited by lower grade tumors (p-value, 0.001). (Table 1)

This inverse relation was further proven by correlation coefficient analysis where GATA3 was found significantly correlated with tumor characteristics. Larger tumor size was inversely related to lower GATA3 levels (r) -.481. Similarly, advanced nodal status was related to lesser GATA3 level and vice versa (r) -.620. Moreover, tumor grade was also contrariwise related with GATA3 levels (r) -.538. (Table 2) All these correlations were significant with correlational coefficient p value of <0.05.

The association of GATA3 levels were also checked with Estrogen, Progesterone and HER2Neu receptor status with chi square test in the study. Estrogen positivity was associated with higher GATA3 levels (p-value 0.001). However Progesterone and HER2Neu receptors statuses did not show any significant association with GATA3 levels, with p-values of 0.27 and 0.57 respectively, which were not significant (Table 1).

To further validate this correlation, the mean values of GATA3 were also correlated with the mean values of ER, PR and HER2Neu receptor status by using independent sample t-test. This was done to further identify any diminutive relations between the variables. Positive ER was found significantly associated with a high mean GATA3 values (p-value 0.01), while patients with either positive or negative status of PR and HER2Neu showed similar mean GATA3 values. Hence negating any association between these receptor status and mean GATA3 values, with a p-value of 0.441 for PR and p-value of 0.557 for HER2neu .

Table 1:- Association of tumor size, nodal status and histological grade according to GATA3 findings using chi square test.

	GATA3= 0 (n=15)	**GATA3=1 (n=15)**	**GATA3=2 (n=4)**	**GATA3=3 (n=4)**	**GATA3=4 (n=12)**	**p-value**
Tumor size						
T1	0 (0.0%)	0 (0.0%)	2 (50.0%)	2 (50.0%)	5 (41.7%)	0.008
T2	7(46.6%)	4 (26.7%)	2 (50.0%)	0(0.0%)	3 (25.0%)	
T3	4(26.7%)	10 (66.7%)	0 (0.0%)	2 (50.0%)	3 (25.0%)	
T4	4 (26.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (8.3%)	
Nodal status						
N0	2 (13.3%)	0 (0.0%)	0 (0.0%)	3 (75.0%)	9 (75.0%)	0.001
N1	2 (13.3%)	1 (6.7%)	1 (25.0%)	1 (25.0%)	2 (16.7%)	
N2	6 (40.0%)	9 (60.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	
N3	5 (33.3%)	5 (33.3%)	1 (25.0%)	0 (0.0%)	1 (8.3%)	
Histological Grade						
Grade 1	2(13.3%)	1 (6.7%)	1(25.0%)	4(100.0%)	10(83.3%)	0.000
Grade 2	6 (40.0%)	2 (13.3%)	2 (50.0%)	0 (0.0%)	1 (8.3%)	
Grade 3	7(46.6%)	12(80.0%)	1 (25.0%)	0 (0.0%)	1 (8.3%)	
ER						
Negative	9 (60)	13 (86.7%)	1 (25.0%)	0 (0.0%)	2 (16.7%)	0.001
Positive	6 (40)	2 (13.3%)	3 (75.0%)	4 (100.0%)	10 (83.3%)	
PR						
Negative	8 (53.3)	4 (26.7%)	1 (25.0%)	0 (0.0%)	5 (41.7%)	0.27
Positive	7 (46.7%)	11 (73.3%)	3 (75.0%)	4 (100.0%)	7 (58.3%)	

HER2Neu						
Negative	7 (46.7%)	6 (40.0%)	3 (75.0%)	1 (25.0%)	7 (58.3%)	0.57
Positive	8 (53.3%)	9 (60.0%)	1 (25.0%)	3 (75.0%)	5 (41.7%)	

Table 2:- Correlation coefficients of GATA3 and Tumor characteristics as size, nodal status, grade, ER ,PR and HER2neu status

	Tumor size	Nodal status	Grade	ER	PR	HEr2 Neu
GATA3	-.484**	-.620**	-.538**	.475**	.104	-.081
Tumor size	1	.482**	.487**	-.551**	-.270	.316*
Nodal status		1	.668**	-.511**	-.157	-.037
Grade			1	-.593**	-.055	.121
ER				1	.417**	-.240
PR					1	.113
HEr2 Neu						1

Correlation is significant at the 0.01 level (2-tailed).
Correlation is significant at the 0.05 level (2-tailed).

Discussion:-

Breast cancer is the most common malignancy in females, so there is an immense need to study different parameters of breast cancer which can help reduce morbidity and mortality of the disease.[3]This led us to conduct a study on GATA3, which is coming up as a novel prognostic marker in breast cancer. Our study will help to increase the utility of GATA3 in prognostication of breast carcinoma.

This study had same mean age population 52.8 ±10.9 as in previous studies done on GATA3 by Rohit Mehra and brandi C et al. [13][14].

Our study showed an inverse relation of GATA3 with tumor size , histological grade and nodal status of the disease, all these results are also shown in studies conducted by Rohit Mehra and brandi C et al, later on David Voduc also replicated these results .[15][13][16]Their study population was larger and had longer follow up durations. Our study reciprocating the same results with smaller sample size further strengthens the utility of GATA3 to be used as prognostic marker in breast carcinoma.

In our study commonest grade was grade 3 while study done by aya m.ismail et al in Egypt showed grade 1 being the commonest grade.[17] This could be a reason for late stage presentation of disease in our patients due to aggressive nature of the disease in our population.

This study showed low levels of GATA3 in ER negative breast cancer and high levels in ER positive. This is in concordance with the results showing inverse relation of ER with GATA3 by a study done in Michigan by varambally et al, Renee V. HOCH and Wei Yan [13][18][19]as ER is an established prognostic marker in breast carcinoma, these results may guide for utilization of GATA3 to be used as a future prognostic marker in breast carcinoma. Further followup will be done at 5 years to determine GATA3 association with survival.

However, This study failed to show any relation of GATA3 with PR status in our study population these results were contrary to study done by varambally et al, who showed significant correlation between GATA3 and PR status. but in their detailed survival analysis curves review, this correlation did not translate in OS benefit for their patients.[13] This lack of evidence for OS can in fact signify our study results.

Also, correlation of GATA3 with HER2neu receptor status was not statistically significant which is similar to results given by Manal I. Abd-Elghany and Aya M. Ismail Et al [17][20]. But a study done by mehra et al showed inverse relation of HER2neu with GATA3 the reason for these contrary results could be that HER2neu was done via immunohistochemistry in our study and studies showing comparable results but study done by mehra et al had done HER2neu with FISH. It has been shown in previous studies discordance occurs in HER2 neu results when performed with IHC or FISH in which FISH being the preferred method.[21]

Study constrains include single institutional study which could be potentiated in future by multi institutional based randomized studies with greater number of enrolled patients.

Conclusion:-

This study concludes that GATA3 expression can be used as a prognostic marker of breast cancer, by showing a significant correlation of GATA3 levels with tumor size, nodal status, tumor grade and ER status. However, relation of GATA3 levels with PR and HER2Neu receptor status further needs to be explored.

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