EVALUATION OF KI67 PREDICTIVE ROLE AND ITS DISCORDANCE BETWEEN PRETHERAPY BIOPSY AND POST THERAPY SURGICAL SPECIMEN IN BREAST CANCER PATIENTS RECEIVING NEOADJUVANT CHEMOTHERAPY.

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ABSTRACT:

Background: *Neoadjuvant chemotherapy (NAC) in breast cancer patients provides an excellent model for evaluation of potential predictive factors. Both clinical complete response (cCR) and pathological complete response (pCR) achieved after neoadjuvant chemotherapy is a surrogate marker for a favorable prognosis. Factors capable of predicting response such as the proliferation marker Ki67 may help improve our understanding of the drug response and its effect on the prognosis and survival.*

Aim of the work: *The aim of this study is to investigate the predictive value of the pretreatment Ki67 regard its ability to predict response to neoadjuvant chemotherapy and to investigate potential differences in proliferation scores between pretreatment core biopsies and post treatment final surgical samples in response to neoadjuvant chemotherapy.*

Patients & methods: *A Retrospective Study conducted on sixty (60) eligible Female Patients with Non metastatic Breast Cancer patients receiving neoadjuvant chemotherapy. in the period from January 2015 till January 2020 at breast clinic unit at Ain-Shams University Hospitals Clinical Oncology department. All Patient characteristics, clinical and pathological data and immunohistochemistry analysis and treatment related data were thoroughly collected.*

Results: *Pretreatment Ki-67 didn't show any significant difference with both clinical complete response (cCR) and pathological complete response (pCR) (all P > 0.05). A significant decrease in Ki-67 expression from a median 25% in core biopsy prior to therapy to 12 % in surgical specimen after NAC in non-pathological complete response (pCR) patients (P = 0.0006)*

Conclusion: *Pretreatment K-i67 level Couldn't play a predictive role in predicting both clinical and pathological complete response. A significant change in Ki-67 expression was observed between core biopsy and surgical specimen after neoadjuvant chemotherapy in breast cancer patients*

Key words: *Breast cancer · Tumor response · Molecular subtypes · Neoadjuvant chemotherapy · Ki67*

INTRODUCTION:

Proliferation is a key feature of tumor progression and is now widely estimated by the IHC, using Ki-67 antibodies. Recently MIB-1 is the most widely used antibody against the Ki-67. Ki-67 expression is usually

estimated as the percentage of tumor cells positively stained by the antibody, with nuclear staining being the most common criterion of positive. High Ki-67 is a sign of poor prognosis associated with a good chance of clinical response to chemotherapy[(1)]**.** The use of Ki67 as a prognostic and predictive marker has been always an interesting topic for discussion in both the neoadjuvant and adjuvant settings [(2)]**.** Several studies reporting the value of Ki-67 to predict response (clinical and/or pathological) to chemo-therapy in early or locally advanced breast cancer found that higher Ki-67 was associated with better response. It is important to note that while high scores of Ki-67 are associated with higher chance of response to chemotherapy, high Ki-67 is a marker of poor prognosis overall. However, good clinical response, particularly pathological complete response, is associated with good long-term prognosis[(1)]**.** Taken together, the results suggest that if a tumor does not respond to chemotherapy, increased Ki67 is a poor prognostic marker. In contrast, in chemotherapy-responding tumors, this effect is not observed anymore, and there is even a tendency that increased Ki67 is linked to improved prognosis. The biological explanation for this is that there are three different groups of tumors: Low proliferating tumors that are not responding to chemotherapy but have a good prognosis anyway (low Ki67 linked to good outcome), high proliferating tumors that are therapy sensitive, high Ki67 is linked to an increased chance of pCR and improved survival (high Ki67 linked to good outcome) and high proliferating tumors that are chemotherapy resistant, increased Ki67 is linked to reduced survival (high Ki67 linked to poor outcome)[(3)].

AIM OF THE WORK:

The aim of this study is to investigate the predictive value of the pretreatment Ki67 regard its ability to predict response to neoadjuvant chemotherapy and to investigate potential differences in proliferation scores between pretreatment core biopsies and post treatment final surgical samples in response to neoadjuvant chemotherapy.

PATIENTS & METHODS:

This is a retrospective study conducted at Clinical oncology and nuclear medicine Department, Ain Shams University Hospitals during the period from January 2015 to January 2020. It included sixty (60) eligible Female Patients with Non metastatic Breast Cancer patients receiving neoadjuvant chemotherapy who met the Eligibility and Exclusion criteria. This study population includes Female patients aged above 18 years old with Histological proven breast cancer with any molecular subtype and according to TNM staging includes T_2, T_3, T_4 with any lymph nodal states and all included Patients received neoadjuvant chemotherapy combined Anthracycline and Taxanes based regimen +/- Trastuzumab in HER2 positive Patients and All included patients had their Ki-67 levels examined both on pretherapy core biopsy and post therapy surgical specimens. This study population excludes Male patients, Bilateral Breast, Inflammatory breast cancer, according to TNM staging: T_2N_0 and Stage IV disease.

Statistics:

The differences in clinic pathological characteristics between clinical or pathological responders and non-responders were calculated with the chi-squared or Fisher's exact test as appropriate. Changes in expression levels of Ki67 biomarker before and after chemotherapy were examined with the Wilcoxon matched pairs test and Mann–Whitney test as appropriate. In this study, P value less than 0.05 was regarded as significant in statistical respect and every P value was two-sided. The collected data will be analyzed using SPSS software statistical computer package. For each variable, the

range, mean and standard deviation will be calculated.

Ethical Considerations:

The protocol of this thesis was approved by the Research Ethics Committee of Ain Shams University. All data obtained from patients will be used for scientific purposes only. Throughout this research, patients' confidentiality was maintained.

RESULTS:

The characteristics of the patient enrolled in this study and their correlations are shown in table (1), (2), (3) and (4). There was no significant difference in clinic pathological characteristics that include age groups, menopausal state, tumor size, IHC (ER, HER2 and KI67) between cCR and non- cCR, all didn't demonstrate a significant response to NAC in statistical results (all P > 0.05). However, patients with positive PR showed significant cCR (P = 0.040) as in table 5 and 6 There was no significant difference in clinic pathological characteristics that include age groups, menopausal state, IHC (ER, PR and Ki-67) between pCR and non- pCR, all didn't demonstrate a significant response to NAC in statistical results (all P > 0.05). Patients with HER2 positive and tumor size ≤ 5 cm seemed to be associated with better pCR rate than patients with HER2 negative and tumor size >5 (P= 0.019 and P = 0.008**,** separately). Out of twenty-one patients with tumor size >5, two patients (9.5%) were in the pCR group vs fifteen patients (38.5%) out of thirty-nine patients with tumor size ≤ 5. Out of twenty-three patients with HER2 positive, eleven patients (47.8%) were in the pCR group vs six patients (16.2%) out of thirty-seven patients with HER2 negative as in table 7 and 8.

In core biopsy, the Ki-67 levels was ≥ 20 in forty-two patients 70 % and The Ki-67 levels was < 20 in eighteen patients 30 %. In surgical specimen, the Ki-67 levels was ≥ 20 in twenty patients 33.33 % and The Ki67 levels was < 20 in twenty-three patients 38.3 and 17 patient was undetermined 28.3% as shown in table (3). High Ki-67 expression in the specimens changed from 67.4% (29/43) to 46.5% (20/43). Low Ki-67 expression in the specimens changed from 32.6% (14/43) to 53.5% (23/43). The Ki-67 index was significantly higher in the core needle biopsy and lower in the surgical specimen. The expression of Ki67 between core biopsy and surgical specimen was found to have statistically significant difference (P = 0.0117) as shown in table (9)

Table 1: Patient characteristics

		N	%
Age	≤ 50 years	37	61.7%
	>50 years	23	38.3%
Medical Comorbidities	Positive	20	33.33%
	Negative	39	65 %
	Undocumented	1	1.66%
Menstrual history	Perimenopausal	4	6.66 %
	Premenopausal	33	55 %
	Postmenopausal	22	36.66 %
	Undocumented	1	1.66%
Family history	Positive	14	23.33%
	Negative	38	63.33%
	Undocumented	8	13.33%
Total		60	100%

Table 2: Assessment of IHC (ER, PR and HER2) on Core biopsy

Core Biopsy IHC		N	%
E.R.	Negative	10	16.7%
	Positive	50	83.3%
P.R.	Negative	9	15.0%
	Positive	51	85.0%
HER2	Negative	37	61.7%
	Positive	23	38.3%
Total		60	100.00%

Table 3: Assessment of Ki-67 on core biopsy and surgical specimen after NAC

Ki-67 Assessment		N	%
Pre Ki-67 on Core Biopsy	Low KI67 < 20	18	30 %
	High KI67 ≥ 20	42	70%
Post Ki-67 on Surgical specimen	Low KI67 < 20	23	38.33%
	High KI67 ≥ 20	20	33.33%
	Undetermined	17	28.33%
Total		60	100.00%

Table 4: Assessment of Clinical and Pathological response after NAC

		N	%
Clinical Response	Clinical complete response (cCR)	8	14.8%
	Clinical Partial response (cPR)	45	83.3%
	Clinical stable disease (cSD)	1	1.6%
	Undocumented	6	10%
Pathological Response	Pathological Complete Response (pCR)	17	28.3%
	Pathological Partial Response (pPR)	37	61.7%
	Pathological Progressive Disease (pPD)	3	5.0%
	Pathological Stable Disease (pSD)	3	5.0%
Total		60	100.00

Table 5: Relationship between tumour size and cCR

Tumour size (cm)	cCR		Total	P value
	N	%	N	
≤ 5	6	15.4%	39	0.623
>5	2	9.5%	21	
Total	8		60	

Table 6: Relationship between IHC and cCR

IHC		cCR		Total	P value
		N	%	N	
ER status	Negative	3	30.0%	10	0.230
	Positive	5	10.0%	50	
PR status	Negative	1	11.1%	9	0.040
	Positive	7	13.7%	51	
Her2 status	Negative	3	8.1%	37	0.227
	Positive	5	21.7%	23	
Pre-Ki67 expression	≤ 20%	2	11.1%	18	0.205
	> 20%	6	14.3%	42	
	Total	8		60	

Table 7: Relationship between tumour size and pCR

Tumour size (cm)	pCR		Total	P value
	N	%	N	
≤ 5	15	38.5%	39	0.019
>5	2	9.5%	21	
Total	17		60	

Table 8: Relationship between IHC and pCR

IHC		pCR		Total	P value
		N	%	N	
ER status	Negative	5	50.0%	10	0.098
	Positive	12	24.0%	50	
PR status	Negative	3	33.3%	9	0.703
	Positive	14	27.5%	51	
Her2 status	Negative	6	16.2%	37	0.008
	Positive	11	47.8%	23	
Pre-Ki67 expression	≦ 20%	4	20%	20	0.550
	>20%	13	32.5%	40	
	Total	17		60	

Table 9: Change of Ki67 value in core biopsy and surgical specimen

Biomarker		Ki67 Core biopsy		Ki67 surgical specimen		McNemar test
KI67		N	%	N	%	
	≥ 20	29	67.4%	20	46.5%	P = 0.0117
	< 20	14	32.6%	23	53.5%	
		43		43		

DISCUSSION:

In the current study as regard complete clinical response, there was no significant difference in clinicopathological characteristics that include age, menopausal state, tumor size and IHC (ER, HER2 and Ki-67) between cCR group and non cCR group, all didn't demonstrate a significant response to NAC (P >0.05 for all). Only patients with positive PR had significant cCR than patients with negative PR (P= 0.040). As regard complete pathological response, there was no significant difference in clinicopathological characteristics that include age, menopausal state and IHC (ER, PR and Ki-67) between pCR group and non pCR group (P >0.05 for all). However, Patients with HER2 positive and tumor size less than or equal to 5 cm seem to be associated with better pCR rates than patients with HER2 negative and tumor size above 5 cm (P=0.019, P= 0.008 separately).

Sanchez-Munoz et al (2010) conducted a study on Seventy-three patients who were treated a combination of epirubicin and cyclophosphamide followed by paclitaxel and gemcitabine and trastuzumab when indicated in a sequential and dose-dense schedule as neoadjuvant chemotherapy. In contrast to our study there was a significant association between pCR and patients with tumors that were hormonal receptor (ER and PR) negative and positive for Ki67 (≥ 20) (P=0.001 for both). In our study patients with ER negative and PR negative and high KI67 and HER2 positive was associated with better pCR than patients with ER positive and ER positive and low KI67 and HER2 negative however this was insignificant may be due to small sample size. ***Bo, De-qi Yang, et al.***

(2008) conducted a retrospective study on one hundred and thirty-five BC patients who were treated with neoadjuvant anthracycline and taxanes regimen. In consistent to our study no significant association was found between cCR and other biological factors (ER and Ki-67) (P=0.210, P=0.260, separately and no significant association between pretreatment Ki-67 and pCR were found (P=0.650). However, HER2 overexpression was a predictive of pCR (P= 0.010). In contrast to our study there was no significance association between cCR and PR (P=0.097) and absence of ER and PR expression was a predictive of pCR (P=0.002, P=0.001, separately). In our study patients with ER negative and PR negative was associated with better pCR than patients with ER positive and ER positive however this was insignificant may be due to small sample size.

Petit, T., et al. (2004) conducted a retrospective study on one hundred nineteen BC patients who were treated by neoadjuvant anthracycline-based regimen. In consistent to our study HER2 overexpression showed no association with cCR (P=0.67). In contrast to our study Absence of hormonal receptor expression (ER and PR) and high Ki-67 was a predictor of cCR (P= 0.003, P= 0.002, separately). Overexpression of HER2 was not predictive of pCR (P=0.99). Absence of hormonal receptor expression (ER and PR) and high Ki-67 was a predictor of pCR (P= 0.008, P= 0.01, separately). ***Chen, Rui, et al. (2018)*** conducted a retrospective study on one thousand and ten BC patients who had undergone anthracycline and taxane-based NAC. In consistent to our study Patients with tumor size less than 4 cm were more probable to attain pCR (P= 0.039). In contrast to our study patients with negative ER and PR and high pretreatment Ki67 (≥ 14%) are more probable to attain pCR (P<0.001, P<0.001, P<0.001, separately). However, HER2 overexpression wasn't a predictor of pCR (P=0.0233). ***Kim, Kwan Il, et al. (2014)*** included seventy-four BC patients who received neoadjuvant anthracycline-based chemotherapy. Similar to our study no significant correlation between cCR and biological markers expression (ER and HER2) (P=0.277 and P=0.092 separately) and the pCR was significantly higher in patients with a HER2-positive status (P=0.040) and was higher in PR negative patients but this was insignificant (P=0.040). In contrast to our study high Ki-67 expression level was a significant factor for predicting better cCR (P<0.001) and no significance association between cCR and PR (P=0.185) and the pCR was significantly higher in patients with ER-negative status (P=0.031) and a higher Ki-67 expression level (P=0.036).

Jin, Soyoung, et al. (2013) conducted a study on two hundred seventy-three patients were treated with neoadjuvant chemotherapy. In consistent to our study the pretreatment Ki-67 expression failed to show an association with pCR (P=0.545). In contrast to our study patients with ER negative and PR negative were associated with better pCR (Both P < 0.001) and HER2 overexpression failed to show an association with pCR (P=0.361). Another study conducted by ***Ingolf, et al. (2014)*** on seventy-seven patients who collectively were divided into 3 groups depending on the cut-off values for Ki-67 (≤15%, 15–50%, and >50%) and investigated the predictive value of Ki-67 for the success of neoadjuvant chemotherapy by correlating it to the pathological response. In consistent to our study there were no significant differences between the 3 groups concerning the number of patients with pCR (P= 0.896). Although our study used a different cutoff point for Ki-67 (≥ 20 and < 20).Also, ***Fasching, Peter A., et al. (2011)*** conducted a study on five hundred fifty-two patients who were treated with different regimens of chemotherapy and using a cut off value of > 13% for Ki-67 expression. In consistent to our study pCR rates were higher in tumors with HER2 overexpression (P< 0.00001). In contrast to our study pCR rates

were higher in tumors with ER and PR negative tumors and high pretreatment Ki-67 level (P< 0.00001 for all).

The presented data showed that Ki-67 index was significantly higher in the core needle biopsy and lower in the surgical specimen. High Ki-67 expression in the specimens changed from 67.4% to 46.5%. The expression of Ki67 between core biopsy and surgical specimen was found to have statistically significant difference (P = 0.0117). Similar to our study ***Ge, Wen-kai, et al. (2015)*** found that high Ki-67 expression in the specimens changed from 45.6% to 15.2%. Ki-67 expression rates decreased significantly after NAC (P < 0.05). A significant decrease in Ki-67 with neoadjuvant chemotherapy was noticed in our study from a median 25% in core biopsy prior to therapy to 12% in surgical specimen after therapy (P = 0.0006) which consistent with ***Bottini et al. (2001)*** conducted a study on total of 152 BC patients where the median number of cells per tumor expressing the Ki67 antigen fell from 16% at the initial biopsy to 8% at surgery. A moderate but highly significant relationship was found between Ki67 values before chemotherapy and those evaluated afterwards (P< 0.001). Another retrospective study conducted by ***Dede, D. S., et al. (2013)*** on 63 BC patients where ki67 Expressions in the preoperative and postoperative status of Ki-67 were compared. Ki-67 values decreased from 10 to 1% following NAC and this decrease was statistically significant (P<0.001). Also, ***Li, Xi-ru, et al. (2011)*** conducted a study on 220 BC patients where the median Ki-67 proliferation index was dramatically decreased after NAC from 35 to 15% (P = 0.036).

Conclusion:

Pretreatment Ki-67 level weren't able to play a predictive role in predicting both clinical and pathological complete response.to neoadjuvant chemotherapy. A significant change in Ki-67 expression between core biopsy and surgical specimen after NAC was found.

Conflict of interest:

The authors declare that they have no conflict of interest.

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تقييم الدور التنبئي لـ Ki67 واختلافه بين العينه السابقة للعلاج والعينة الجراحية بعد العلاج في مرضى سرطان الثدي الذين يتلقون العلاج الكيميائي ما قبل الجراحة

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خلفية: يوفر العلاج الكيميائي ما قبل الجراحة (NAC) في مرضى سرطان الثدي نموذجا ممتازا لتقييم العوامل التنبؤية المحتملة. كلا من الاستجابة السريرية الكاملة (cCR) والاستجابة الكاملة المرضية (pCR) التي تحققت بعد العلاج الكيميائي ما قبل الجراحة يعتبر علامة بديلة لتشخيص إيجابي. قد تساعد العوامل القادرة على التنبؤ بالاستجابة مثل علامة الانتشار Ki٦٧ في تحسين فهمنا للاستجابة الدوائية وتأثيرها على التشخيص والبقاء على قيد الحياة.

الهدف من العمل: الهدف من هذه الدراسة هو التحقيق في القيمة التنبؤية للمعالجة المسبقة Ki٦٧ فيما يتعلق بقدرتها على التنبؤ بالاستجابة العلاج الكيميائي ما قبل الجراحة والتحقيق في الاختلافات المحتملة في درجات الانتشار بين الخزعات الأساسية قبل المعالجة والعينات الجراحية النهائية بعد العلاج استجابة العلاج الكيميائي ما قبل الجراحة.

المرضى والطرق: دراسة بأثر رجعي أجريت على ستين (٦٠) مريضة مؤهلة مصابة بسرطان الثدي غير النقيلي تتلقى علاجا كيميائيا ما قبل الجراحة. في الفترة من يناير ٢٠١٥ حتى يناير ٢٠٢٠ بوحدة عيادة الثدي بمستشفى جامعة عين شمس بقسم الأورام الإكلينيكي. تم جمع جميع خصائص المريض والبيانات السريرية والمرضية وتحليل الكيمياء المناعية والبيانات المتعلقة بالعلاج بدقة.

النتائج: لم تظهر المعالجة المسبقة Ki-٦٧ أي فرق كبير مع كل من الاستجابة السريرية الكاملة (cCR) والاستجابة الكاملة المرضية (pCR) (جميعها $P > ٠,٠٥$). انخفاض كبير في تعبير Ki-٦٧ من متوسط ٢٥٪ في الخزعة الأساسية قبل العلاج إلى ١٢٪ في العينة الجراحية بعد NAC في مرضى الاستجابة الكاملة غير المرضية (pCR) ($P = ٠,٠٠٠٦$)

الخلاصة: مستوى المعالجة المسبقة K-i٦٧ لا يمكن أن يلعب دورا تنبؤيا في التنبؤ بالاستجابة الكاملة السريرية والمرضية. لوحظ تغيير كبير في تعبير Ki-٦٧ بين الخزعة الأساسية والعينة الجراحية بعد العلاج الكيميائي المساعد الجديد في مرضى سرطان الثدي