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Breast Panel Biomarker Changes After Neoadjuvant Chemotherapy in Breast Cancer: A Single-center Study

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ABSTRACT

Objectives. The aim of this study is to evaluate the breast panel biomarker changes and tumor intrinsic subtype after neoadjuvant chemotherapy among patients with residual invasive breast carcinoma whose breast specimens were processed at St. Luke's Medical Center - Quezon City (SLMC-QC) from 1 January 2017 to 30 June 2023.

Methodology. Cases of residual invasive breast carcinoma status post neoadjuvant systemic therapy were identified by retrospective review of cases. The baseline characteristics, type of biopsy and resection procedures, pre – and post–neoadjuvant ER, PR and HER2 status and pre – and post–neoadjuvant tumor intrinsic subtype were analyzed using frequency and percentage. The comparison of the changes in pre- and post-neoadjuvant breast panel biomarkers were analyzed by using McNemar test while the changes in the intrinsic tumor subtype was done using Wilcoxon signed-rank test.

Results. This study encompassed a total of 43 cases of residual invasive breast carcinoma following neoadjuvant systemic therapy. The data disclosed shifts in the breast molecular profile and intrinsic subtype post-administration of neoadjuvant systemic therapy. The alterations in hormone receptor status, ER and PR, were observed in 11.6% of cases, while HER-2 status exhibited changes in 2.3%. A 14% change in the tumor intrinsic subtype is observed. Among the initial 18 Luminal A cases, 1 transitioned to Luminal B, and among the 6 Luminal B cases, 2 become HER2 enriched subtypes. Furthermore, among the initial 12 HER2 enriched cases, three shifted to Luminal B, while all triple-negative cases remained unchanged after chemotherapy.

Conclusion. Based on our findings, alterations in the molecular profile of breast tumors, including shifts in intrinsic subtype after neoadjuvant chemotherapy (NAC), could impact patient prognosis. While the data generated from this study may not exhibit statistical significance, its clinical relevance is noteworthy. In summary, retesting of breast biomarkers in the resection specimen is recommended to accurately ascertain the appropriate use of targeted therapy.

Key words: residual invasive breast carcinoma, neoadjuvant systemic therapy, breast panel

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INTRODUCTION

Neoadjuvant chemotherapy (NACT) for invasive breast carcinoma is the standard of care for locally advanced and an alternative option for primary operable invasive breast carcinoma (IBCA). Changes in biomarker expression after neoadjuvant chemotherapy have been recorded, with an average prevalence rate reaching up to 18% for estrogen receptor, 32% for progesterone receptor, and 6% for HER2/Neu.[1,2] Currently, there is no universally agreed-upon guideline for the retesting of these biomarkers post-neoadjuvant chemotherapy, leading to considerable variability in practices.

A global working group was assembled to formulate practical guidelines for the pathological evaluation of residual disease in neoadjuvant clinical trials for breast cancer. The group suggests that the retesting of ER, PR, and HER2 should be based in the initial biopsy testing results, the pathological characteristics of the remaining tumor, and the potential influence on treatment decisions.[3] In 2020, a survey involving 26 pathologists across the United States revealed that 15 out of 25 respondents engage in routine retesting of NACT samples. Primarily,

the retesting of breast biomarkers was initiated either in response to clinical requests from oncologists or as a necessity dictated by clinical trial protocols.[4]

This study aimed to evaluate the breast panel biomarkers and tumor intrinsic subtype changes among patients with residual invasive breast carcinoma after neoadjuvant systemic therapy in a single center.

METHODOLOGY

This is an observational, descriptive, cohort, single-center study. This study was approved by the Institutional Ethics Review Committee (IERC) of St. Luke's Medical Center – Quezon City (SLMC-QC).

Patient selection

Eighty-six (86) cases of residual invasive breast carcinoma status post neoadjuvant systemic therapy were identified by retrospective review of cases from the records of surgical pathology reports in the laboratory information system from January 2017 to June 2023. The specimens include tissue breast biopsies (core needle, mammotome, incision), total mastectomies, modified radical mastectomies, needle localization excision surgeries, breast panel by immunohistochemical stains (IHC) and/or HER2 fluorescence in situ hybridization (FISH). To be included in this study, the following inclusion criteria were observed: (1) the breast specimens should have been processed or slides were reviewed at SLMC-QC; (2) patient's should have received neoadjuvant systemic therapy and must have residual invasive breast carcinoma on resection surgery; (3) all cases must have pre and post neoadjuvant breast biomarkers by IHC; and/or FISH, (4) the patient must have undergone partial mastectomy, total mastectomy, and or modified radical mastectomy. Patients of all groups were included. Cases with equivocal HER2/c-ERB result and with incomplete data in the laboratory information system were excluded.

Data analysis

Determination of the breast hormonal biomarker changes of post neoadjuvant chemotherapy were analyzed. Frequency and 95% confidence interval of the percentage were calculated. The significance of the change of hormonal biomarkers in pre-neoadjuvant chemotherapy and post- neoadjuvant chemotherapy was determined using McNemar test. The level of significance was set at $\alpha = 0.5$.

RESULTS

A total of 43 breast cancer patients with residual invasive tumor after receiving neoadjuvant systemic therapy were included in the study whose mean age is 53 years old (SD=11.5) while most common biopsy is via core needle (88.4%) and 9.3% are via incision. Around 93% of them underwent modified radical mastectomy while 4.7% had total mastectomy (Table 1).

Data on the estrogen receptor status (ER) reveals that prior to neoadjuvant chemotherapy, 48.8% were positive for ER, but it slightly increased to 55.8% after. Specifically, 11.6% of cases had changes in ER, but this difference is not significant (p =.375). Among the 21 positive ER in pre-NACT, only 1 turns out to be negative after treatment, while among the 22 negative ER in pre-NACT, 4 of them become positive (Table 2).

Data on the progesterone receptor status (PR) reveals that prior to neoadjuvant chemotherapy, 48.8% were positive for PR, but it slightly decreased to 46.5% after. Specifically, 11.6% of cases had changes in PR, but this difference is not significant (p = 1.000). Among the 21 positive PR in pre-NACT, 3 turn out to be negative, while among the 22 negative PR in pre-NACT, 2 become positive (Table 3).

The data on HER2 reveal that prior to neoadjuvant chemotherapy, 41.9% were positive for HER2 but it slightly increases 44.2% after. Specifically, 2.3% of cases had changes in HER2, but this difference is not significant (p=1.000).

Table 1. Profile of Breast Cancer Patient

	Values
Age (years), mean ± SD	53.0 ± 11.5
Sex, n, %	
Female	43 (100)
Biopsy, n, %	
Core needle biopsy	38 (88.4)
Mammotome biopsy	1 (2.3)
Incision biopsy	4 (9.3)
Surgery, n, %	
Total mastectomy	2 (4.7)
Modified Radical Mastectomy	40 (93.0)
Needle localization excision biopsy	1 (2.3)

Table 2. Changes in ER pre- and post-neoadjuvant chemotherapy

ER		N	%
Pre-NACT ER	Positive	21	48.8
	Negative	22	51.2
Post-NACT ER	Positive	24	55.8
	Negative	19	44.2
Change in ER	Yes	5	11.6
	No	38	88.4

Pre-NACT (Pre-neoadjuvant chemotherapy); Post-NACT (Post-neoadjuvant chemotherapy)

Pre-NACT ER	Post-NACT ER		*p* value
	Positive	Negative	
Positive	20	1	0.375
Negative	4	18	

Pre-NACT (Pre-neoadjuvant chemotherapy); Post-NACT (Post-neoadjuvant chemotherapy)

Table 3. Changes in PR pre- and post-neoadjuvant chemotherapy

PR		n	%
Pre-NACT PR	Positive	21	48.8
	Negative	22	51.2
Post-NACT PR	Positive	20	46.5
	Negative	23	53.5
Change in PR	Yes	5	11.6
	No	38	88.4

Pre-NACT (Pre-neoadjuvant chemotherapy); Post-NACT (Post-neoadjuvant chemotherapy)

Pre-NACT PR	Post-NACT PR		*p* value
	Positive	Negative	
Positive	18	3	1.000
Negative	2	20	

Pre-NACT (Pre-neoadjuvant chemotherapy); Post-NACT (Post-neoadjuvant chemotherapy)

Table 4. Changes in HER2 pre- and post-neoadjuvant chemotherapy

HER2		n	%
Pre-NACT HER2	Positive	18	41.9
	Negative	25	58.1
Post-NACT HER2	Positive	19	44.2
	Negative	24	55.8
Change in HER2	Yes	1	2.3
	No	42	97.7

Pre-NACT (Pre-neoadjuvant chemotherapy); Post-NACT (Post-neoadjuvant chemotherapy)

Pre-NACT HER2	Post-NACT HER2		*p* value
	Positive	Negative	
Positive	18	0	1.000
Negative	1	24	

Pre-NACT (Pre-neoadjuvant chemotherapy); Post-NACT (Post-neoadjuvant chemotherapy)

Table 5. Changes in Sub-Type pre- and post-neoadjuvant chemotherapy

Subtype		n	%
Pre-NACT Subtype	Luminal A	18	41.9
	Luminal B	6	14.0
	HER2 enriched	12	27.9
	Triple negative breast CA	7	16.3
Post-NACT Subtype	Luminal A	17	39.5
	Luminal B	8	18.6
	HER2 enriched	11	25.6
	Triple negative breast CA	7	16.3
Change in Subtype	Yes	6	14.0
	No	37	86.0

Pre-NACT (Pre-neoadjuvant chemotherapy); Post-NACT (Post-neoadjuvant chemotherapy)

Pre	Post				*p* value
	Luminal A	Luminal B	HER2 enriched	Triple negative	
Luminal A	17	1	0	0	1.000
Luminal B	0	4	2	0	
HER2 enriched	0	3	9	0	
Triple negative	0	0	0	7	

All 18 positive remains to be positive while the 24 negative prior, 1 becomes positive after chemotherapy (Table 4).

Table 5 displays the molecular subtypes and their alterations. The predominant subtype before neoadjuvant chemotherapy is Luminal A (41.9%), followed by HER2-enriched (27.9%). Post-chemotherapy, Luminal A decreased to 39.5%, and HER2 decreased to 25.6%. Specifically, 6 out of 43 cases (14%) underwent changes, but this change did not reach statistical significance (p=1.000). Among the initial 18 Luminal A cases, one transitioned to Luminal B, and among the 6 Luminal B cases, two shifted to HER2-enriched. Furthermore, among the initial 12 HER2-enriched cases, three transitioned to Luminal B, while all triple-negative cases remained unchanged after chemotherapy.

DISCUSSION

Currently, there is no universally adopted reporting system for post-neoadjuvant chemotherapy breast carcinoma, and data from current practices show substantial diversity in the retesting of tumor biomarkers following neoadjuvant therapy.[5] According to the 2023 NCCN guidelines for invasive breast carcinoma, the status of ER/PR and HER2 may undergo changes during treatment and metastatic progression. In such cases, it is recommended to consider repeat testing on fresh samples, especially if it would lead to a modification of the treatment approach.[6]

Results from this study revealed that there are alterations in the molecular profile and subtypes of invasive breast carcinoma following neoadjuvant systemic therapy. The observed rates of change in hormone receptors, ER and PR, were both 11.6%, aligning with the deduced findings of Sahoo et al.,[5] of 3% to 8% across reported studies. Furthermore, HER2 status exhibited less frequent changes (1% to 7%) compared to hormone receptors in response to systemic treatment.[2,7-9] The discrepancy in biomarker status between pre-treatment and post-treatment tumors can be attributed to various factors. These include preanalytical variables such as cold ischemia, intratumoral heterogeneity, unsampled tumor regions, and the influence of targeted therapy. More precisely, this refers to situations in which HER2-positive tumors may change to HER2-negative state after receiving HER2-targeted treatments.[5]

Out of the total of 43 cases, only 6 cases (14%) had alterations in the molecular intrinsic subtype after NACT. However, these alterations did not achieve statistical significance, as indicated by a *p*-value of 1.000. Out of the original 18 cases classified as Luminal A, one case changed to Luminal B. Additionally, out of the 6 cases initially classified as Luminal B, two cases changed to HER2-enriched. In addition, out of the original 12 cases classified as HER2-enriched, three cases converted to Luminal B subtype, while all cases classified as triple-negative remained stable during chemotherapy.

Based on these findings, one case developed HER-2 expression. This case is of a 30-year-old female with a Luminal A type of tumor (ER+, PR+, HER2-) and was classified as Luminal B (ER+, PR+, HER2+) in the resection specimen. The patient received 4 cycles of paclitaxel prior to definitive surgery.

Another noteworthy case from this study involves a 72-year-old female who developed a second breast mass with exhibiting distinct histologic and molecular profile that is seen on the modified radical mastectomy specimen. The initial biopsy indicated a HER-2 enriched molecular subtype (ER-, PR-, HER2+), but upon excision, two masses were identified. One mass retained the HER-2 enriched type, while the other mass exhibited a Luminal A subtype (ER+, PR+, HER2-). The second mass may represent a synchronous malignancy that may or may not be present at the initial time of biopsy.

A clinically significant shift in ER, PR, or HER2 status from negative to positive post-neoadjuvant chemotherapy (NAC) might necessitate a modification in adjuvant treatment. For instance, if the initially reported hormone status changes from ER negative to positive, the patient could become eligible for endocrine therapy. Similarly, if the reported biomarker status shifts from HER2 negative to positive, the patient could become a candidate for trastuzumab. However, if there is no alteration in biomarker status or if the reported differences are not clinically relevant, then repeating the testing becomes an additional unnecessary healthcare cost.[8]

CONCLUSION

According to our results, changes in the molecular profile of breast tumors, including shifts in intrinsic subtypes after neoadjuvant chemotherapy (NAC), may influence patient prognosis. Although the data from this study may not demonstrate statistical significance, its clinical relevance is significant. In summary, retesting of breast biomarkers in the resection specimen is recommended to accurately ascertain the appropriate use of targeted therapy. Further research should be pursued to enhance our understanding of the biology and treatment strategies for breast cancer patients.

To optimize cost-effectiveness in resource-constrained settings, adherence to the recommendations of the I-SPY pathology working group is advised, wherein repeat testing is advocated for tumors with unknown or ambiguous biomarker status and if it is necessary for clinical trials. Repeat testing may be warranted for tumors demonstrating heterogeneity, those with multiple tumors with distinct histomorphology, and cases where tumors failed to respond to treatment.[5]

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declare no conflict of interest.

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