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Clinical and Pathologic Tumor Response Following Response-guided Neoadjuvant Chemotherapy for Locally-advanced Breast Cancer in a Tertiary Hospital Breast Center in the Philippines

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Rationale/Objective: Neoadjuvant chemotherapy (NAC) is recommended for locally-advanced breast cancer (LABC) to improve resectability and provide in-vivo tumor response assessment. This study aimed to describe the clinical and pathologic tumor response of LABC patients after response-guided NAC.

Methods: This is a retrospective cohort analysis of 128 LABC patients who underwent NAC using sequential doxorubicin/cyclophosphamide (AC) – docetaxel (T) regimen at the Philippine General Hospital Breast Care Center. Clinical and pathologic response rates were analyzed according to clinicopathologic variables including tumor intrinsic subtype.

Results: Objective clinical response (complete and partial) was observed in 88% (111/128) of patients with 11% (14/128) achieving pathologic complete response (pCR). The hormone receptor-negative/Her2-enriched (HR-/Her2+) subtype had the highest pCR rate (23.5%) followed by triple negative subtype (HR-/Her2-) at 19%. The hormone receptor-positive/Her2-positive (HR+/Her2+) subtype had the lowest pCR (4.7%). Two patients with initial poor response to AC but had good response upon shifting to T achieved pCR. Twelve patients (9.4%) had poor response to AC and T chemotherapy. Patients who were pre-menopausal (p=0.04), had ductal histology (p=0.03), with a HR-/Her2- (p=0.002) or HR+/Her2+ subtype (p=0.03) had good response to AC. Intrinsic subtype was not significantly associated with treatment response in those who received docetaxel. There was strong association between the pathologic and clinical responses (Spearman's Rho score 0.69, p-value <0.0001).

Conclusion: Clinical and pathologic response to NAC was highly dependent on tumor subtype. Clinical response was predictive of pathologic response. Response-guided NAC allowed direct and early evaluation of tumor treatment response that allowed for treatment modifications.

Key words: breast cancer, neoadjuvant therapy, chemotherapy

Breast cancer is the most common malignancy in the Philippines for both sexes with an annual incidence of 24,798 cases per 100,000 of the population.[1] Many of the breast cancer cases in the country are diagnosed at later stages which may be due to the inability of most patients to afford the direct and indirect costs of diagnosis and treatment, related socioeconomic impediments, and the lack of awareness.[2]

Locally-advanced breast cancer (LABC) includes patients with 1) operable disease at presentation, 2) inoperable disease at presentation, and 3) inflammatory breast cancer. Treatment typically includes neoadjuvant systemic therapy followed by surgery and radiotherapy.[3]

Results from National Surgical Advuant Breast and Bowel Project (NSABP) B-18 trial showed no statistically significant differences in disease free survival (DFS) and overall survival (OS) when chemotherapy is given on a neoadjuvant or adjuvant basis.[4] However, the neoadjuvant approach has advantages that are particularly important for LABC: tumor downstaging and *in vivo* tumor response assessment to chemotherapy. NSABP B-27 results demonstrated that preoperative taxane added to an anthracycline-based neoadjuvant chemotherapy (NAC) regimen significantly increased the proportion of patients having pathologic complete response (pCR).[4] Additionally, patients who achieved pCR appear to have significantly superior survival outcomes compared with patients who did not.[4,5] With the goal of increasing the chances of achieving pCR, intended chemotherapy

regimens are preferably completed prior to surgery when neoadjuvant approach is undertaken.

Although giving chemotherapy in a neoadjuvant setting may have the disadvantage of missing out on the opportunity for locoregional control should disease progression occur during treatment, real-time monitoring of the change in tumor burden is an important feature that can allow tailoring of treatment. Tumor shrinkage and time to disease progression are both important endpoints in clinical management of patients and cancer clinical trials.[6]

At the University of the Philippines - Philippine General Hospital Breast Care Center (UP-PGH BCC), a clinical response-guided approach to NAC is being applied. Subsequent chemotherapeutic cycles are either continued or discontinued and shifted to another drug depending on clinical response assessed mid-course of the regimen. A previous study in the institution showed a low pCR rate of 4.8% to an anthracycline-based NAC regimen.[7] Changes have since been made to the NAC protocol-based on recent evidence.

This study aimed to describe the clinical and pathologic tumor response following clinical response-guided NAC using the sequential anthracycline (doxorubicin/cyclophosphamide, AC) and taxane-based (docetaxel, T) chemotherapy. Additionally, the study aimed to determine the clinical and pathologic tumor responses according to intrinsic tumor subtype and number of NAC cycles received, characteristics of patients with good mid-cycle response to AC and T, the likelihood of response to T after poor response to AC, and the correlation between clinical and pathologic tumor response.

Methods

Study Design and Study Population

This was a retrospective cohort study of LABC patients who underwent NAC using sequential doxorubicin/cyclophosphamide (AC) and docetaxel (T) regimen (AC→T regimen) at the UP-PGH BCC.

Included in this study were all biopsy proven breast cancer patients ≥18 years old, clinically staged IIIA-IIIC (American Joint Committee on Cancer Staging [AJCC] 8th edition) who underwent NAC using standard AC→T regimen followed by modified radical mastectomy or radical mastectomy from July 2013 to June 2018.[8]

Patients who were male, with metastatic disease, bilateral breast cancer, prior history of breast or non-breast malignancy or chemotherapy, received Her2-targeted treatment (trastuzumab and/or pertuzumab), with significant delay in chemotherapy (>6 weeks from last NAC cycle) and time to surgery (>8 weeks from last NAC cycle), and who failed to complete chemotherapy cycles due to other medical conditions, adverse drug reactions and/or financial limitations were excluded. Candidates for NAC underwent standard metastatic work up consisting of chest radiograph, liver ultrasound, and bone scan. To avoid confounding the analysis, patients who received Her2-targeted therapy were excluded due to the inconsistency in its administration preoperatively for economic and access reasons.

Eligible patients were identified through a search in the database and conference reports of the UP-PGH Department of Surgery. Relevant data were retrieved from medical records, surgical pathology and immunohistochemistry reports.

Treatment Details

Drug dosages were computed based on the standard regimen: doxorubicin (A) 60mg/m^2 concurrent with cyclophosphamide (C) 600mg/m^2 given as IV infusion on day 1 and repeated every 21 days for 4 cycles followed by docetaxel (T) 75mg/m^2 given as infusion every 21 days for 4 cycles.

The tumor size, determined by caliper measurement of palpated tumor, was measured at baseline prior to start of 1st cycle of NAC, subsequently prior to each cycle, and after the last cycle prior to surgery. The surface area of the tumor was the product of the longest diameter and the greatest perpendicular diameter. Tumor response rate was the percentage difference of the baseline tumor surface area and tumor surface area immediately prior to administration of due dose of chemotherapy. Mid-course assessment of tumor response was done prior to administration of 3rd cycle of each component of the sequential NAC regimen (prior to 3rd cycle of AC and prior to 3rd cycle of T). Overall tumor response rate was obtained after the last cycle of NAC and represents the

percentage decrease in area of tumor compared to baseline tumor size measured pre-neoadjuvant chemotherapy.

Clinical tumor response was categorized into complete response (complete disappearance of primary tumor and involved nodes), partial response (at least 50% decrease in the size of the primary tumor), no response (less than 50% decrease in size or increase in size by less than 25%), or progressive disease (increase in size by ≥25% or appearance of new lesions).[9] The response in the lymph nodes was not quantified. Appearance of new breast lesions or increase in burden of nodal disease (e.g. appearance of supraclavicular nodes) were considered progressive disease. At mid-course of AC (before giving 3rd AC cycle), if at least a partial response was not achieved then patient was shifted T, foregoing completion of rest of AC cyles. Similarly, if there is no partial response at least after 2 cycles of T, patient was scheduled for surgery if tumor was resectable and without distant metastasis. Patients still deemed unresectable but non-metastatic were presented to a multidisciplinary conference for disposition (either surgery, next line NAC with or without targeted therapy, neoadjuvant hormonal therapy or radiotherapy). If at any time, there was progressive disease clinically, patient was shifted to the next component of the NAC regimen (if on AC shifted to T; if on T proceeded to surgery).

Study Variables

The following variables and categories were used in the analysis: age (<35, 35-50, >50 years), menopausal status (premenopausal, postmenopausal) clinical stage (cIIIA, cIIIB, cIIIC), clinical tumor size (<5cm, ≥5cm), clinical nodal status (N0, N1, N2, N3), molecular subtype (hormone receptor-positive/Her2-negative [HR+Her2-], hormone receptor-positive/Her2-positive [HR+Her2+], hormone receptor-negative/Her2-positive [HR-Her2+/Her2-enriched], hormone receptor-negative/Her2-negative [HR-Her2-]/triple-negative breast cancer [TNBC]), clinical tumor response (stable disease, partial response, complete response, progressive disease), pathologic stage (pCR, pI, pIIA, pIIB, pIIIA, pIIIB, pIIIC), pathologic tumor size (pT0, pT1, pT2, pT3, pT4), pathologic nodal status (pN0, pN1, pN2, pN3), histologic grade (1,2,3), lymphovascular invasion (positive, negative), perineural invasion (positive, negative), margin status (negative, positive), and extent of completion of neoadjuvant chemotherapy cycles (completed, AC complete/T incomplete, AC incomplete/T complete, AC incomplete/T incomplete). Hormone receptor (HR) positivity was defined as at least 1% cells staining positive for either estrogen (ER) or progesterone receptor (PR). Her2 positivity was defined as immunohistochemical staining (IHC) score of +3 or IHC score +2 with amplification on fluorescence in situ hybridization study (FISH). Patients were also categorized as responders and non-responders, with those who had complete and partial response considered responders while those with stable disease and disease progression considered as non-responders. Clinical response rate was defined as percentage of patients achieving partial and complete clinical response while tumor response rate referred to the percentage reduction in tumor size. Pathologic complete response (pCR) was defined as absence of residual invasive and non-invasive disease on the breast and lymph nodes (ypT0 ypN0).

Statistical Analysis

Statistical analysis was performed using the Stata version 13 (Statacorp LLC, Texas USA). The baseline patient characteristics and outcomes were presented as tables of frequencies and percentages or means and standard deviations. Odds ratio was used to compare the clinical and pathologic tumor response according to intrinsic subtype and number of chemotherapy cycles received. The same statistical analysis was used to determine the difference in clinicopathologic variables in patients who were good or poor responders. A statistically significant difference was considered if the p-value is less than 0.05. To demonstrate the correlation of clinical and pathologic responses, a scatter plot was used to show the possible association between two quantitative variables. A Spearman's Rank Correlation Analysis was used to determine the strength of association.

Ethical Consideration

This was a non-interventional study. The study was initiated after protocol approval from the University of the Philippines Manila Research Ethics Board (Protocol Code [SUR] 2018-273-01).

Results

Among the patients who underwent neoadjuvant chemotherapy for locally advanced breast cancer from 2013 – 2018, 197 records were retrieved. Fifty-one records had incomplete clinical data. Eighteen patients were excluded due the following reasons: bilateral breast malignancy (2), significant delay in surgery (5), different chemotherapy regimen used (9) and metastatic disease after chemotherapy (2). No patient was excluded due to receipt of trastuzumab or pertuzumab preoperatively. A total of 128 patients were included in this study (Figure 1).

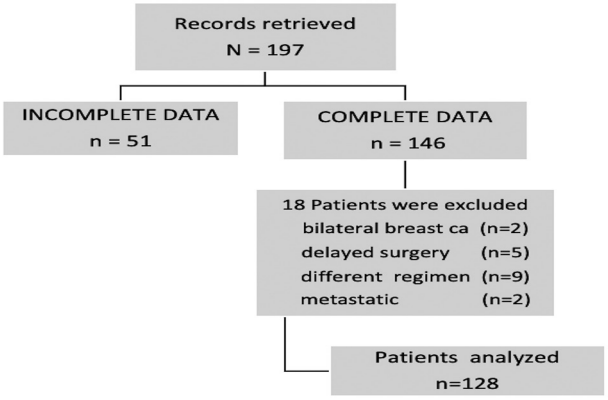

Figure 1. Data collection flow chart.

The mean age of the study population was 49 years (SD 9.2) with a range of 32 to 71 years. Majority of patients were between 35-50 age group and 52% (67) were post-menopausal. The predominant histology was invasive ductal carcinoma (89%). Half of the tumors (52%) were HR+Her2-. HR+Her2+ and TNBC tumors were next most common comprising 16% each. Her2-enriched were least common at 13%. The mean tumor size was 12.3 cm (SD 4.8) and ranged from 4.5 cm to 28 cm in their widest diameter. Majority (91%) of patients were clinical stage IIIB on presentation (Table 1).

Objective clinical response (complete and partial clinical response) was seen in 88% of patients with mean tumor response rate of 80%. HR+Her2- patients had the least reduction in tumor size and clinical response rate. Fourteen (11%) patients achieved pCR. The pCR rate was highest among patients with HR-Her2+ subtype (23.5%) despite not receiving neoadjuvant Her2-targeted therapy followed by TNBC subtype (19%) (Table 2).

Table 1. Baseline characteristics of patients undergoing neoadjuvant chemotherapy.

Clinicopathologic Variable	Frequency (%) n=128
Age	
<35 years	9 (7%)
35-50 years	66 (51.6%)
>50 years	53 (41.4%)
Menopausal Status	
Pre-menopausal	61 (47.7%)
Post-menopausal	67 (52.3%)
Histology	
Ductal	114 (89.1%)
Mucinous	7 (5.5%)
Lobular	3 (2.3%)
Apocrine	1 (0.8%)
Tubular	1 (0.8%)
Unknown	2 (1.6%)
Clinical Stage	
Stage IIIA	6 (4.7%)
Stage IIIB	116 (90.6%)
Stage IIIC	6 (4.7%)
Clinical Tumor Size (cm)	
≤5cm	3 (2.3%)
>5cm	125 (97.7%)
Clinical Nodal Status	
N0	23 (18%)
N1	62 (48.4%)
N2	37 (28.9%)
N3	6 (4.7%)
Tumor Subtype	
Hormone Receptor Positive/Her2-neu Negative (HR+Her2-)	67 (52.3%)
Hormone Receptor Positive/Her2-neu Positive (HR+Her2+)	21 (16.4%)
Hormone Receptor Negative/Her2-neu Positive (HR-Her2+)	17 (13.3%)
Triple Negative (TNBC)	21 (16.4%)
Unknown	2 (1.6%)
Clinical Tumor Response	
Complete Clinical Response	19 (14.8%)
Partial response	94 (73.4%)
Stable disease	14 (10.9%)
Progressive disease	1 (0.78%)
Pathologic stage	
pCR	14 (10.9%)
Stage I	8 (6.3%)
Stage IIA	10 (7.8%)
Stage IIB	19 (14.8%)
Stage IIIA	14 (10.9%)
Stage IIIB	51 (39.8%)
Stage IIIC	12 (9.4%)
Pathologic tumor size (cm)	
0	14 (10.9%)
≤2	20 (15.6%)
2 - 5	52 (40.6%)
>5cm	42 (32.9%)
Pathologic lymph node status	
0	58 (45.3%)
1-3	36 (28.1%)
4-9	23 (18%)
≥10	11 (8.6%)
Histologic Grade	
1	10 (7.8%)
2	44 (34.4%)
3	30 (23.4%)
Not reported	44 (34.4%)
Lymphovascular space invasion	
Yes	60 (46.9%)
No	33 (25.8%)
Not reported	35 (27.3%)
Perineural Invasion	
Yes	18 (14.1%)
No	14 (10.9%)
Not reported	96 (75%)
Margin status	
Negative	124 (96.9%)
Positive	4 (3.1%)

Table 2. Clinical and pathologic tumor responses following neoadjuvant chemotherapy (NAC) according to intrinsic subtype and extent of NAC regimen completion.

PARAMETER	N	CLINICAL TUMOR RESPONSE						PCR
		Complete Response	Partial Response	Stable Disease	Progressive Disease	Clinical Response Rate	Mean Response Rate	
All Patients	128	19	94	14	1	88.8%	80.1%	14 (10.9%)
INTRINSIC SUBTYPE								
HR+ Her2-	67	7 (10.4%)	49 (73.1%)	11(16.4%)	0	83.5%	74.6%	5 (7.5%)
HR+ Her2+	21	4 (19%)	17 (81%)	0	0	100%	89.9%	1 (4.8%)
HR- Her2+	17	3 (17.6%)	13 (76.5%)	1 (5.9%)	0	94.2%	84.4%	4 (23.5%)
TNBC	21	5 (23.8%)	13 (61.9%)	2(9.5%)	1 (4.8%)	85.7%	84.0%	4 (19%)
Unclassified[a]	2	0	2 (100%)	0	0	100%	85.1	0
EXTENT OF NAC COMPLETION (No. of cycles)								
Completed (8)	63	18 (28.6%)	45 (71.4%)	0	0	100%	93.3%	12 (19%)
AC complete T incomplete (6)	9	0	6 (66.7%)	2 (22.2%)	1 (11.1%)	66.7%	66.1%	0
AC incomplete T complete (6)	44	1 (2.3%)	43 (97.7%)	0	0	100%	76.7%	2 (4.5%)
AC incomplete T incomplete (4)	12	0	0	12 (100%)	0	0%	32.2%	0

[a]Two patients with unclassified tumor subtype due to equivocal Her2 result. One is HR+ and the other is HR-.Unclassified cases not included in the computation of *p* values.

Those who completed the planned 8 cycles of chemotherapy had an average mean clinical tumor response of 93.3% with a pCR rate of 19%. Interestingly, two patients who had initial poor response to AC but had good response upon shifting to T achieved pCR. None of the patients who had initial good response to AC but poor response to T and poor response to both AC and T achieved pCR. There were 12 (9.4%) patients who had poor response to both AC and T chemotherapy with their mean tumor response being only 32.2% (Table 2).

At mid-course, 56% of patients were responders to AC compared to 84% for docetaxel. Half of the patients with HR+ tumors (44/88) were non-responders to AC compared to 12.5%(11/88) for T (Table 3). After non-response to AC, there is a 78.6% likelihood of good response to T (95%CI 65.5-87.6%) (Table 4).

A comparison of the clinicopathologic variables in early responders and non-responders (Table 3) showed that patients who were postmenopausal were more likely to have poor response to AC compared to pre-menopausal patients (OR 0.48, p=0.04). Patients with ductal histology were more likely to have good response to AC than those with tubular or mucinous histologies (OR 10.65, p=0.03). Compared to HR+Her2- tumors, tumors that were TNBC (OR 7.86, p=0.002) or HR+Her2+ (OR 3.28, p=0.03) were more likely to have good clinical response to AC chemotherapy. Patients aged 35-50 years were significantly more likely to have good clinical response to docetaxel chemotherapy (OR 6.1, p=0.03). Ductal histology was also associated with better response to docetaxel than non-ductal histology (OR 5.73, p=0.03).

Positive association between clinical and pathologic tumor responses was demonstrated in the study as shown by the scatter plot in Figure 2. A Spearman's rho score of 0.69 (p-value <0.0001) was computed indicating a strong association between the two variables.

Table 4. Response to docetaxel (T) after midcourse non-response to doxorubicin/cyclophosphamide (AC)

Response to T	Likelihood	95% Confidence Interval
Good	78.57%	65.49% - 87.63%
Poor	21.43%	12.37% - 34.51%

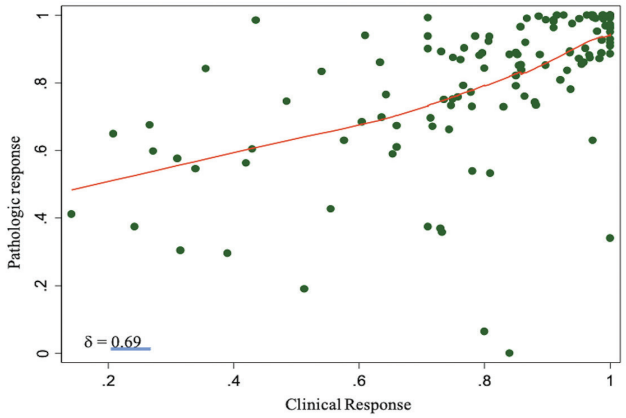

Figure 2. Association between clinical and pathologic tumor response.

Discussion

Neoadjuvant chemotherapy is a valuable strategy in locoregionally-advanced breast cancer management as it allows for tumor downstaging and surgical de-escalation, provides insight into prognosis with achievement of pCR, and provides opportunity to evaluate individual tumor sensitivity and tailor therapy.[4,5,10,11,12]

NAC was applied in the study patients primarily to improve the operability of the tumors rather than facilitate breast conservation surgery. With mean tumor size of 12.3 cm and most having skin involvement and heavy nodal burden, even with good response to NAC, all patients required at least a modified radical mastectomy. The surgical advantage of NAC in some patients was the avoidance of complex surgical wound closure.

If the need for chemotherapy is clear even without the prognostic information from the histopathology of definitive surgical specimen, giving the chemotherapy preoperatively rather than postoperatively is preferrable to maximize the opportunity to achieve pCR. The pCR has been identified as a potential surrogate marker of improved survival on individual patient level.[4,5,13] In a pooled analysis of 12 international NAC trials, complete eradication of tumor from the breast and lymph nodes was associated with improved event-free survival (HR 0.44, 95%CI 0.39-0.51) and overall survival (HR 0.36, 95% CI 0.3-0.44) compared to those with residual disease.[5] However, value of pCR as a trial-level surrogate for

Table 3. Characteristics of clinical responders and non-responders to neoadjuvant chemotherapy.

CHARACTERISTICS	DOXORUBICIN / CYCLOPHOSPHAMIDE				DOCETAXEL			
	Responders n=72	Non- responders *n*=56	Odds Ratio	*P value*	Responders n=113	Non- Responders n=15	Odds Ratio	*P value*
Age								
<35	6 (8.3%)	3 (5.4%)	*ref*	-	6 (5.3%)	3 (20%)	*ref*	-
35-50	42 (58.3%)	24 (42.3%)	0.88	0.86	61 (54%)	5 (33.3%)	6.10	*0.03
>50	24 (33.3%)	29 (51.8%)	0.41	0.24	46 (40.7%)	7 (46.7%)	3.29	0.15
Menopausal status								
Pre-menopausal	40 (55.6%)	21 (37.5%)	*ref*	-	55 (48.7%)	6 (40%)	*ref*	-
Post-menopausal	32 (44.4%)	35 (62.5%)	0.48	*0.04	58 (51.3%)	9 (60%)	0.7	0.53
Histology								
Ductal	70 (97.2%)	46 (83.6%)	10.65	*0.03	105 (92.9%)	11 (78.6%)	5.73	*0.03
Lobular	1 (1.4%)	2 (3.6%)	3.5	0.44	3 (2.7%)	0	-	-
Mucinous/Tubular	1 (1.4%)	7 (12.7%)	*ref*	-	5 (4.4%)	3 (21.4%)	*ref*	-
Tumor Intrinsic Subtype								
HR+Her2-	29 (40.8%)	38 (69.1%)	*ref*	-	56 (50.5%)	11 (73.3%)	*ref*	-
HR+Her2+	15 (21.1%)	6 (10.9%)	3.28	*0.03	21 (18.9%)	0	*omit*	-
HR-Her2+	9 (12.7%)	8 (14.5%)	1.48	0.48	16 (14.4%)	1 (6.7%)	3.14	0.29
TNBC	18 (25.4%)	3 (5.5%)	7.86	0.002	18 (16.2%)	3 (20%)	1.18	0.82
Grade								
1	3 (7%)	7 (17.1%)	*ref*	-	9 (12.3%)	1 (9.1%)	*ref*	-
2	22 (51.2%)	22 (53.7%)	2.33	0.26	39 (53.4%)	5 (45.5%)	0.87	0.90
3	18 (41.9%)	12 (29.3%)	3.50	0.11	25 (34.2%)	5 (45.5%)	0.56	0.61
Tumor size (cm)								
≤5cm	2 (2.8%)	1 (1.8%)	*ref*	-	3 (2.7%)	0	*ref*	-
>5cm	70 (97.2%)	55 (98.2%)	0.64	0.71	110 (97.3%)	15 (100%)	1.01	-
Response to AC								
Good response	-	-	-	-	69 (61.1%)	3 (20%)	1.84	
Poor response	-	-	-	-	44 (38.9%)	12 (80%)	*ref*	

long term survival has not been definitely established thereby requiring further assessment of endpoints like event-free survival and overall survival to clearly define clinical benefit of novel neoadjuvant therapies.[5,14,15]

The pCR rate of 11% in this study was higher than the previously reported 4.8% pCR rate in the same institution.[7] This could be due to the addition of taxane and completion of the planned chemotherapy regimen preoperatively. Previously, NAC protocol in the institution consisted of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) regimen with 4 cycles given preoperatively and 2 cycles postoperatively.[7] Findings from the NSABP-27 which showed doubling of pCR rates with addition of taxane and giving the entire regimen preoperatively have led to the revision in the NAC protocol in UP-PGH BCC.[4] In the present study, non-response to AC part of the NAC regimen was seen in 56% of patients compared to just 15% with T. Additionally, among patients who were non-responders to AC but were responders to T, objective clinical response was still achieved in 79% of patients (44/66) with mean tumor response rate still high at 77% and pCR still achieved in 4.5% of patients. Several studies on LABC showed superior objective tumor response with addition of taxane in NAC regimen.[16,17,18] In the Aberdeen trial on NAC, patients who had objective clinical response to anthracycline-based regimen after 4 cycles were either continued to 4 more cycles of same regimen or shifted to 4 cycles of T.[18] Patients given T had higher objective clinical response and pCR.[18]

This study's pCR rate which used definition of ypT0 ypN0 was consistent with the pooled pCR rate of 13% reported in the the CTNeoBC meta-analysis of 12 international trials that included 11955 patients.[5] However, the rate is much lower than the 19% reported using the US National Cancer Database (US NCDB) that included close to 14,000 women, the largest study so far reporting on response rates and predictors thereof.[19] This could be due to differences in disease stages included, percentage distribution of breast cancer subtype, and neoadjuvant systemic therapy received. The US NCDB study included all stages while the current study focused on locoregionally-advanced disease. However, a high pCR rate can still be achieved even with LABC, as shown by another study that included only LABC with a reported 25% pCR rate.[10] The study concluded that extent of disease did not predict pCR and similar rates of pCR as with early breast cancer was achievable.[10] Other studies confirmed that there is no difference in NAC response by tumor stage after adjustment for other variables.[20,21]

The response rate to NAC is related to its primary tumor subtype as defined by the expression of the hormone receptors (estrogen [ER] and progesterone receptors [PR]) and Her2-neu receptor.[10,19] Breast cancer tumor can be broadly categorized into molecular subtypes namely luminal A, luminal B, Her2-enriched and triple negative/basal-like. As per commonly accepted definition, luminal A tumors are ER+ PR+ Her2-, low grade and with low Ki67 score. Luminal B subtype has more variable definition that encompasses ER+PR+Her2- with intermediate or high grade or high Ki67 score, ER+PR-Her2- or ER+PR+Her2+. Her2-enriched are ER-PR-Her2+ while triple negative (TNBC)/basal-like are ER-PR-Her2-.[13,19] In this study, classification of luminal A and B were simplified into HR+Her2- and HR+Her2+ instead as information on grade and particularly Ki67 were not always available. The pCR rates according to molecular subtype in this study was consistent in pattern, although numerically lower, compared with published international reports showing highest pCR rates with Her2-positive disease followed by TNBC and lowest with the luminal subtypes.[10,19] In the US NCDB study, pCR rates were 38.7% for Her2-enriched, 23.2% for TNBC, 8.3% for luminal B and 0.3% for luminal A.[19] In the present study, the higher pCR rate in HR+Her2- tumors compared to the HR+Her2+ tumors could be due to non-receipt of Her2-targeted therapy by the latter and possible inclusion of some "luminal B" tumors in the HR+Her2- category due to limitations in the definition applied. In the two international studies that reported much higher overall pCR rates, proportion of Her2-enriched and TNBC was more than half the study population whereas in this study, HR+ tumors comprised nearly 70%.[10,19] In a multivariable analysis, receptor subtype was found to be an independent predictor of overall pCR with Her2-positive tumors having the best odds of pCR.[10] The association of pCR with long-term survival outcomes was also strongest with the more aggressive subtypes, Her2-enriched and TNBC.[5,13]

Addition of Her2-targeted therapy in the neoadjuvant systemic therapy regimen has further increased pCR rates in Her2-positive disease to as high as 38% with addition of trastuzumab alone and 51.9% with dual blockade with trastuzumab and pertuzumab.[22,23] As such, the low overall and Her2-enriched subtype-specific pCR rates in the UP-PGH BCC can be largely due to non-receipt of Her2-targeted therapy by study patients. This exclusion, while a significant limitation, was necessary in this study due to the very infrequent inclusion of Her2-targeted therapy in the neoadjuvant setting at the time of the study due to economic constraints. The non-administration of Her2-targeted therapy represented the situation in most parts of the country where access to anti-Her2 targeted therapy is severely limited.

Giving the planned chemotherapeutic regimen preoperatively allows real-time monitoring of the response of the tumor to the regimen being given. If there is no clinical response to a particular regimen, another drug or regimen can be chosen or decision can be made to proceed with surgery. Hence, giving of ineffective therapy that has associated side effects can be avoided. This also avoids unnecessary delays in definitive locoregional treatment which is particularly critical in patients with LABC. The UP-PGH BCC has adopted a protocol of clinical response-guided neoadjuvant therapy to maximize this advantage of NAC. Mid-course of AC, if less than 50% response was noted, the rest of the cycles were withheld and the next drug, docetaxel, in the sequential therapy was given. In two clinical trials evaluating clinical response-guided NAC using docetaxel-doxorubin-cyclphosphamide (TAC) and 5-fluororucacil-epirubicin-cyclophosphamide (FEC) respectively, assessment of response after 2 cycles of was deemed adequate to provide information on primary resistance to chemotherapy.[24,25] In the present study, about 44% and 16% of patients had poor response after 2 cycles of AC and T drug regimens, respectively. In the GeparTrio trial, patients who had less than 50% reduction in tumor size following two cycles of concurrent docetaxel, doxorubicin, and cyclophosphamide (TAC) were randomized to receive 4 more cycles of TAC or shifted to cross-resistant regimen of vinorelbine and capecitabine. Key findings were 1) that patients who had good mid-course response to TAC had higher pCR rate compared to poor responders and 2) that there was no improvement in pCR for the poor responders with shifting to another regimen.[11,26,27] Interestingly, despite absence of impact on pCR rates, response-guided NAC was associated with improved disease-free survival but this effect was only evident in subset of hormone receptor-positive disease.[28] It has been suggested that HR+ tumors may be more amenable to response-guided approach.[28] In a study by Wang-Lopez et al, standard NAC regimen consisting of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) for 3 cycles followed by docetaxel (T) for 3 cycles was compared with an adapted strategy of shifting to 2 cycles of T if with less than 50% response rate to first 2 cycles of FEC or 2 cycles of FEC if with more than 50% response after 2 cycles of FEC.[25] Both standard and adapted strategies showed similar pCR rates.[25]

The results of the two studies may call into question the practice of shifting regimens in case of early non-response. However, note that vinorelbine and capecitabine may be inherently inferior to combination of taxane and anthracycline regimen, considered standard and most effective NAC regimen, hence the lack of advantage of shifting the regimen. In the study by Wang-Lopez et al, the lower cumulative number of docetaxel cycles in the adapted strategy may account for the absence of difference in pCR.[25] In the current study, in case of non-response to AC, the patients were shifted to docetaxel, a drug that has consistently shown to effect improvements in objective tumor response and pCR rates when added to a preoperative regimen.[4] In another arm in the Aberdeen trial, patients who had no objective clinical response after 4 cycles of an anthracycline-based regimen were shifted to 4 cycles of T with resulting 55% objective clinical response rate and 2% pCR rate.[18] In this study, after non-response to AC, 67% and 3% had objective clinical response rate and pCR rate, respectively. It is however unclear if there is an advantage to adding T to AC for combined TAC regimen instead of shifting to single agent T in case of poor response and can be the subject of further study. In the BCIRG-005 trial on adjuvant therapy for early breast cancer, sequential (AC→T) or concurrent (TAC) regimen of doxorubicin and docetaxel resulted in similar long-term survival outcomes with similar toxicity profile if appropriate hematologic support was

given to the latter group.[29] Comparing the two regimens in the neoadjuvant setting showed no difference in pCR rates.[30] The latter study, however, did not apply a clinical response-guided approach.

In the study, patients who completed 8 cycles of planed NAC were more likely to achieve pCR than those who completed less than 8 cycles. Conclusions on association of NAC cycles and pCR in this study are confounded by the protocol dictating discontinuation of regimen mid-course in case of non-response. Hence, patients who completed 8 cycles, the good clinical responders, can be expected to have better chance of pCR. Conversely, patients who completed less than 8 cycles had poor clinical response to AC, T or both, making pCR less likely. In the pooled analysis of German neoadjuvant trials, pCR was associated with increased number of chemotherapy cycles and cumulative dosing.[31] The association of number of cycles was strongest for patients with HR+ disease irrespective of Her2 status while the association of cumulative anthracycline dose was strongest for Her2- negative disease. In this study, half of HR+ patients had poor mid-course response to AC. It may be worthwhile to investigate if patients with less than partial response but non-progressive disease can be continued on with 2 more cycles of AC with or without addition of T. As suggested by von Minckwitz et al, response-guided chemotherapy may be further tailored according to subtype.[31]

In this study, the authors, found a positive correlation between clinical and pathologic response. In the GeparTrio trial, pCR rate was four times higher in patients with early clinical response to NAC compared with non-responders.[26,27] The trial identified independent predictors for mid-course response after 2 cycles of TAC to be age <50, grade 3 and HR-negative status, with the latter being the strongest predictor.[21] In this study, premenopausal patients were more likely to have mid-course response to the AC component of the NAC. A possible explanation could be ovarian suppression effect during chemotherapy particularly for HR+ tumors. About 70% of patients in this cohort are HR+. In a study by Ahn et al, clinical response rate to NAC was found to be higher among premenopausal patients who developed chemotherapy-induced ovarian dysfunction (CIOD), although this did not impact pCR rate.[32] The association between clinical response and CIOD was significant particularly in HR+ patients. However, in contradiction to this proposed mechanism, TNBC (HR-Her2-) patients in this study were found to have higher odds of clinical response to AC than HR+Her- patients. For docetaxel, there was no difference in clinical response according to menopausal status. This could be due to the very small number of patients not responding to docetaxel. The status of ovarian function during and following NAC in the current study is unknown and could be the subject of future investigation.

Mid-course clinical response to AC varied according to subtype. Both HR+Her2+ and TNBC had higher likelihood of response to AC compared to HR+Her2- tumor. This is inconsistent with the results of GeparTrio trial showing greater likelihood of response across HR-negative subtypes. There was no difference in clinical response according to tumor subtype for docetaxel. Ductal histology had higher likelihood of response to both AC and T, consistent with reports of its greater association with higher pCR rates compared to other histologies.[27] Young age was identified as a good prognostic factor for NAC response but this was not observed in this report .[21] Age between 35-50 was found to have higher likelihood of response to T compared to patients aged less than 35. For AC, there appears to be a non-significantly higher likelihood of response with younger age.

The study has several limitations including: 1) incomplete or unavailable data on several important prognostic factors such as grade and Ki67 which can improve classification into luminal A and luminal B subtypes, 2) non-administration of targeted therapy for Her2-enriched subtype, and 3) clinical tumor response assessment based on palpation alone. The measurement of tumor dimensions by palpation were subject to intra- and interobserver variability. Breast ultrasonography and mammography have better accuracy in tumor response evaluation following NAC compared to palpation.[24,33] However, given the size of the tumors, palpation provided the most practical and affordable assessment method in this study despite its inherent limitations.

This observational study cannot make definitive conclusions as to the effectivity of the response-guided approach to NAC adapted in the institution. A randomized trial with a control arm of completing planned chemotherapeutic regimen without clinical

response monitoring can best address the issue but may be inappropriate especially in cases of progressive disease. Further study on response-guided NAC can be explored for patients with stable disease. Additional investigations can be done on 1) the appropriate timing to assess interim response to NAC, 2) adding T to AC for combined TAC regimen instead of complete discontinuation of the latter in case of non-response, and 3) study impact of neoadjuvant Her2-targeted therapy with the improved access to the drug recently. A significant limitation of this study is the assumption of pCR as a true surrogate marker for survival. To be more informative, the survival outcomes associated with this response-guided approach need to be verified.

Conclusion

In conclusion, addition of taxane and completion of planned NAC regimen improved clinical and pathologic tumor response. Likelihood of clinical and pathologic response was highly dependent on tumor subtype. Patients with midcourse response to NAC were more likely to have pathologic complete response. Clinical and pathologic responses were positively correlated. Neoadjuvant chemotherapy allows direct and early evaluation of tumor response that can lead to more tailored approach to individual patient treatment.

Conflicts of Interest Statement

The authors declare that they have no conflict of interest.

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