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Original Research

Neoadjuvant Systemic Therapy for Locally Advanced Breast Cancer in St. Luke's Medical Center: 10-Year Local Experience and Response Rates

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Background: Neoadjuvant therapy has given important prognostic and predictive information based on pathologic response as seen on studies showing that pathologic complete response (pCR) is associated with favorable disease-free and overall survival in some molecular subtypes. The main objective is to determine the pCR rate among patients with locally advanced breast cancer (LABC) in our institution.
Method: A total of 259 patients with LABC who received neoadjuvant therapy and underwent definitive surgery at St. Luke's Medical Center Quezon City from 2007 to 2017 were retrospectively analyzed through chart review.
Results: Patients' median age at diagnosis was 51 years old. 57% were premenopausal and 42% were postmenopausal. The most common histology was Invasive Ductal at 92%. The most common subtype was Luminal/HER2 negative (52%). Majority of the patients have Stage III disease. The most common chemotherapy regimen used was sequential Anthracycline and Taxane (AC/EC/FEC then Taxane with or without Trastuzumab and Docetaxel with or without Trastuzumab followed by FEC) at 31%, Anthracycline-based (Doxorubicin or Epirubicin with Cyclophosphamide/5FU -EC/ AC/FAC) at 28%, and concurrent Anthracycline-based and Taxane (TAC/AT/ET) at 27%. Of the 95 patients with Her 2 positive disease, 21 (22%) received anti-Her2 blockade as part of their neoadjuvant regimen. The pCR, defined as absence of invasive residual cancer in the breast and axillary lymph nodes, with or without ductal carcinoma-in-situ (DCIS) was seen in 46 patients (18%). Among the patients who achieved pCR, the most common subtype is Luminal/HER2 negative at 17% and the most common regimen used was Docetaxel followed by FEC (5FU+EC) at39%.
Conclusion: Among 259 patients, pCR is achieved in 18% of patients using standard chemotherapy. This study shows that the most common neoadjuvant regimen used was sequential Anthracycline and Taxane and most common subtype is Luminal/Her negative.

Introduction

Breast Cancer is a major public health problem for women throughout the world. In the United States, breast cancer remains the most frequent cancer in women and the second most frequent cause of cancer death [1].

Multiple factors are associated with an increased risk of developing breast cancer, but the majority of these factors convey small to moderate increase in risk for any individual woman. It has been estimated that approximately 50% of women who develop breast cancer have no identifiable risk factor beyond increasing age and female gender [2].

In the Philippines, the identified risk factors for breast cancer are being overweight, having no

children at the age of 30, having a family history of breast cancer, drinking excessive alcohol, and having early menstruation and later menopause, among others [3].

According to the Philippine Cancer Society and DOH data as well as the Philippine Society of Medical Oncology, breast cancer is so common in the Philippines that one in every 13 Filipinas is expected to develop it in her lifetime. Moreover, the Philippines has been identified as among the having the highest incidence rate of breast cancer in Asia [3].

The evaluation of the patient newly diagnosed with breast cancer begins with a determination of operability. Patient known to have metastatic disease and those with locally advanced breast cancer are not candidates for surgery as the first therapeutic approach and should be treated with neoadjuvant therapy [1].

Patients with early breast cancer are typically subjected to definitive surgery first (mastectomy or lumpectomy) followed by adjuvant systemic therapy in the form of endocrine therapy, cytotoxic chemotherapy and anti-HER2 therapy, depending on certain tumor and patient factors. Radiation therapy is also an important adjuvant treatment for early breast cancer to complete the curative treatment. Some patients, however, present with large and fixed tumors or with heavy axillary nodal disease such that upfront surgery is not possible or the chances of a positive margin is very likely. Thus, preoperative or neoadjuvant systemic therapy given, typically in intravenous form, to patients who have locally advanced cancer to render unresectable tumors operable.

The term LABC encompasses patients with (1) operable disease at presentation (clinical stage T3N1),

(2) inoperable disease at presentation (clinical stage T4 and/or N2-3) and (3) Inflammatory Breast Cancer (IBC) (Clinical stage T4dN0-3). These groups of patients carry a substantial risk for metastasis, and as such, should be evaluated by a multidisciplinary team. Treatment includes neoadjuvant chemotherapy, surgery and radiation therapy. Long-term survival was improved with the use of neoadjuvant therapy as part of a trimodal treatment.2 The treatment may be in the form of cytotoxic chemotherapy, endocrine therapy and HER2 targeted therapy, whether concurrently or sequentially with the following goals: (1) To downstage a tumor to allow definitive surgery with adequate and acceptable surgical margins; (2) To allow and improve the rates of Breast Conservation Surgery (BCS) if the woman so desires it; (3) To provide an opportunity to observe in-vivo the clinical, radiologic and pathologic response which allows personalized therapy; and (4) To provide early and immediate systemic control with the main goal of achieving pathologic complete response (pCR), a treatment outcome associated with a more favorable disease free and overall survival [1].

According to international guidelines from the NCCN, ASCO and ESMO, preoperative systemic therapy is indicated in women with locally advanced or inoperable breast cancer particularly those with inflammatory breast cancer, those with N2 and N3 regional lymph node disease; and T3 and T4 tumors.

These patients are considered to have locally advanced breast cancer (LABC), referring to a heterogeneous group of breast cancers without evidence of distant metastasis (M0) and represent only 2% to 5% of all breast cancers in first world countries like the United States, however, based on a 14-year study of 4,260 patients from the Hospital Tumor Registry of SLMC-QC by the Breast Cancer Working group, the incidence may be as high as 20% with the rest being early stage (45%), stage 4 (25%) and pure DCIS or stage 0 (6%) [2,4].

The primary goal of neoadjuvant systemic therapy used to be just to improve resectability and achieve better margins. Currently, however, neoadjuvant treatment can now provide important prognostic information based on actual response to therapy. Studies have shown that for patients with inflammatory breast and locally advanced breast cancer, it is now of prime importance to

achieve pCR after neoadjuvant therapy because it is associated with favorable disease-free (DFS) and overall survival (OS) [1]. Patients who experience pCR have better long-term outcomes with lower risk of cancer recurrence than women with residual cancer following neoadjuvant chemotherapy [2].

A recent metaanalysis on neoadjuvant therapy trials show that the response rates and clinical outcome (DFS and OS) are very much dependent on the molecular subtype of the patient, ie, luminal, HER2 positive, triple negative. It concluded that pCR, as a prognostic marker, seem to be most useful among the triple negative subtypes and the ER negative/PR negative, HER2 positive (clinically HER2 enriched) subtypes and are less useful in predicting outcome for the luminal tumors (ER and PR positive).

To our knowledge, there is limited local data describing the response rates of breast cancer patients to neoadjuvant treatment. The response rates to neoadjuvant systemic therapies are affected and are dependent on multiple factors of a patient's clinical profile at presentation. This is divided into patient factors (age, menopausal status, tumor size, nodal involvement, performance score, presence of co-morbidities, educational attainment and financial status) and tumor factors (specific histology, the histologic and nuclear grade, the presence or absence of Estrogen Receptor (ER) and Progesterone Receptor (PR) and HER2/neu overexpression, proliferative markers like ki67 and the specific clinical molecular subtype for which the tumor is classified and other tumor factors like presence of Tumor Infiltrating Lymphocytes (TILs) and presence of tumor necrosis).

Response rates to neoadjuvant cytotoxic chemotherapy alone, whether in combination using non cross-resistant drugs or whether these drugs are given sequentially, the overall clinical response rate is high, as breast carcinoma is a generally chemosensitive tumor. However, residual invasive cancer after surgery to the breast and the axilla is very common and the rate of pathologic Complete Response (pCR) rate have been historically low at 20-25%. In a local study done by Fournier et al, (2015) on 76 patients who underwent pre-operative treatment, residual invasive cancer was present in almost 90% of these patients, either in the breast, axillary lymph nodes or both [5]. In another local study by Acidera et al, (2004) among 26 patients who underwent neoadjuvant therapy, there was no (0%) pathologic complete response noted using the standard anthracycline and taxane-based cytotoxics [6]. In another study done by Macalindong et al., (2015), Of 63 patients, 54% had LR at 2 years with 263 days mean time to recurrence. Age, pathologic nodes (pN), percent positive pN, pStage, lymphovascular invasion (LVSI), and RT were significant LR predictors on simple logistic regression. pN (OR 1.31, p= 0.01) and RT (OR 0.14, p= 0.004) were independent predictors on multiple logistic regression. In patients without RT, no independent predictor was found [7] (Table 1).

	Population	Intervention	Outcome
Fournier et al (2015) [5]	76 patients	Pre-operative treatment	Residual cancer burden = 90% of patients
Acidera et al (2004) [6]	26 patients	Standard anthracycline and taxane-based neoadjuvant therapy	0% pCR
Macalindong et al (2015) [7]	63 patients	Neoadjuvant therapy	54% had local recurrence at 2 years

Table 1. Previous Local Studies done on Neoadjuvant Treatment.

The use of other forms of neoadjuvant systemic treatments such as endocrine therapy in our institution and globally is also very limited and is not a popular popular approach locally. The recent approval of anti HER2 targeted therapy to cytotoxic chemotherapy has been of limited use also before 2012 but is showing promise when used with cytotoxic chemotherapy among HER2 positive breast cancer subtypes.

Some of the recent landmark trials that has improved pathologic complete response rates were

seen among HER2 expressing breast cancer subtypes, incorporating anti-HER2 therapies like Trastuzumab, Pertuzumab and Lapatinib. The summary of these studies is shown below (Table 2).

	Population	Intervention	Outcome
Noah	Her 2 positive	Trastuzumab + neoadjuvant treatment	3 yr event-free survival 71% with HR 0.59
Neosphere	Her 2 positive	Pertuzumab, Trastuzumab, Docetaxel	Increase in pCR to 16.8%
Tryphaena	Her 2 positive	Pertuzumab, Trastuzumab + chemotherapy± anthracycline	pCR rates 57-66%
Neoallto	Her 2 positive	Lapatinib and/or Trastuzumab	3 yr event-free survival with HR 0.38

Table 2. Published Trials on Neoadjuvant Treatment.

NCCN panel recommends that tumor response should be routinely assessed by clinical exam during the delivery of preoperative systemic therapy. Imaging during preoperative systemic therapy should not be done routinely, but may be considered if tumor progression is suspected.

Our main objective is to determine the pCR rate among patients with locally advanced breast cancer (LABC) in our institution. We also aim to describe the clinical and radiologic response of patients included in this study, describe the treatment protocol administered and enumerate the phenotypic subtype distribution of patients included in this study.

Materials and Methods

Study Population and Data Collection

We retrospectively analyzed patients histopathologically diagnosed to have locally advanced breast cancer who completed neoadjuvant therapy at St. Luke’s Medical Center from January 2007 to May 2017. Patients with locally advanced breast cancer were identified from but not limited to available census, tumor registry, surgical logbooks, clinic logbooks, Ambulatory care unit database. Charts of all patients diagnosed with breast cancer were reviewed.

Neoadjuvant systemic therapy may be in the form of either endocrine only therapy, cytotoxic only therapy, anti-HER2 therapy – single or dual, endocrine + anti-HER2 therapy and cytotoxic + antiHER2 therapy. Patients should have undergone definitive breast surgery with available full histopathologic report. Patients who presented with metastatic disease upon diagnosis were excluded from the study.

This study was approved by the Local Institutional Review Board.

Data analysis

Sample size was calculated based on the Pathologic Complete Response rate among breast cancer patients under neoadjuvant systemic therapy assumed to be 21.5% (Spring et al., 2016), with the maximum allowable error of 5% and reliability of 95%, sample size required is 257 [8].

Results and Discussion

Characteristics of the population study

A total of 259 patients who met the inclusion criteria were included in this study. Baseline

characteristics of included patients are shown in Table 3.

Characteristics	Number of Patients	Percentage
	N=259	(%)
Median Age at diagnosis	51 years	
Menopausal staus		
Pre-menopausal	150	57
Post-menopausal	109	42
AJCC Staging		
Stage IIA	n = 19	7
Stage IIB	n = 68	26
T2 N1 M0	50	19
T3 N0 M0	18	7
Stage IIIA	n = 52	20
T0 N2 M0	1	0.3
T1 N2 M0	2	0.7
T2 N2 M0	6	2
T3 N1 M0	36	14
T3 N2 M0	7	3
Stage IIIB	n = 96	37
T4 N0 M0	34	13
T4 N1 M0	50	19
T4 N2 M0	12	5
Stage IIIC	n = 17	7
Any T N3 M0	17	7
Incomplete Data	7	3
Histologic Type		
Invasive Ductal	239	92
Invasive Lobular	5	2
Other types	17	6
Phenotypic Subtype		
Luminal, Her 2 unknown	13	5
Luminal, Her2 negative	135	52
Luminal, Her2 positive	59	23
Non-luminal, Her2 positive	38	15
Triple Negative	14	5
Ki67	70	
< 20	7	3
≥ 20	63	24
Not done	189	73

Table 3. Baseline Characteristics.

*AJCC NCCN Version 1.2018

Patients' median age at diagnosis was 51 years old. 57% were premenopausal and 42% were postmenopausal. In the latest Breast Cancer Facts and Figures 2017-2018 by the American Cancer Society [9], the 2010-2014 median age of diagnosis was 62. Incidence rates of breast cancer increased over the past years due to mammography screening and women 50 years and older are noted to have increased incidence of breast cancer.

The most common histology was Invasive Ductal at 92% which is consistent with current literature. Majority of the patients have Stage III disease at diagnosis (n=165, 64%). There were 19 patients

who were Stage IIA at diagnosis who underwent neoadjuvant chemotherapy and are included in the analysis. Seven patients were noted to have Stage III disease based on chart review however the available data and work up were not available at the time of data gathering hence proper staging cannot be done.

The most common subtype was Luminal/HER2 negative (52%). Among the Luminal subtype, both Her 2 negative and her 2 positive, 40 have single hormone receptor positive breast cancer. Single hormone receptor positive tumors without Her2 overexpression were associated with poorer survival [10]. Twenty-eight (28) are ER+ and twelve (12) are PR+ only. Seventy-five (75%) of those with PR+ are seen in Luminal Her 2 positive. This was also noted in the study by Chan et al [11] showing that ER (-) and PR (+) phenotype is associated with higher grade with HER2 overexpression and occurs more commonly in younger women and represents a group of more aggressive hormone receptor positive tumors.

Thirteen patients have unknown Her2 status. On seven of these patients, Her 2 testing was not included in the breast panel. All of these patients were diagnosed and underwent surgical treatment before 2010. Prior to this year, Her2 testing was not routinely done for breast cancer patients in developing countries [12]. The establishment of the Scientific Partnership for HER2 testing Excellence (SPHERE) in 2010 promoted and facilitated HER2 testing for both breast and gastric cancer across Asia Pacific [13]. The remaining six patients have equivocal Her2neu tests. Her2 FISH was done on two of them which also turned out to be equivocal. Cytotoxic chemotherapy was administered in all of these patients.

Our study also explored the other pathologic features in patients who underwent neoadjuvant treatment. Ki67, a marker of cancer proliferation, is still not being requested routinely as there is still a lack of standardized procedure for Ki67 assessment [14]. Only 70 patients (27%) underwent Ki67 testing. According to Acs et al [15], the most relevant cut-off value for ki67 was 20% (p=0.002).

Neoadjuvant Treatment

The most common chemotherapy regimen used was sequential Anthracycline and Taxane at 31%. Forty patients received Doxorubicin + Cyclophosphamide followed by Taxane (AC → T), three patients received Doxorubicin + Cyclophosphamide followed by Taxane + Herceptin (AC → TH, 2 patients received Epirubicin + Cyclophosphamide followed by Taxane (EC → T) and 1 patient received Fluorouracil + Epirubicin + Cyclophosphamide followed by Taxane (FEC → T). Thirty five patients received Taxane first followed by Anthracycline, seven of which received Docetaxel + Trastuzumab followed by FEC (TH → FEC) and 35 patients received T →FEC. Anthracycline-based treatment was given in 28% of patients (Doxorubicin or Epirubicin with Cyclophosphamide/5FU -EC/AC/FAC) 28%, and concurrent Anthracycline-based and Taxane (TAC/AT/ ET) at 27% (Table 4).

Neoadjuvant Treatment	N=259	%
Endocrine Treatment	n = 3	
Aromatase inhibitor	3	2
SERM[a]	0	
Cytotoxic Treatment	n = 256	
Anthracycline only	72	28
Taxane only	32	12
Concurrent A + T[b]	71	27
Sequential A + T[b]	81	31

Table 4. Neoadjuvant Treatment Administered.

[a]SERM, Selective Estrogen Receptor Modulators; [b]A,Anthracycline, T, Taxane

Neoadjuvant treatment is an integral part of treatment of patients with locally advanced disease. Multidisciplinary involvement is ideal in mapping out the treatment plan for patients. Standard regimen were used and patients included were able to complete planned treatment.

Of the 97 patients with Her 2 positive disease, 21 (22%) received anti-Her2 blockade as part of their neoadjuvant regimen (Table 5).

Neoadjuvant Treatment	N = 21	%
AC→TH[c]	3	14
TH[d]	9	43
TCH[e]	1	5
TH→FEC[f]	7	33
Ptz + H + D[g]	1	5

Table 5. Cytotoxic Treatment with Anti-Her2 Blockade.

[c]Doxorubicin + Cyclophosphamide→ Paclitaxel + Trastuzumab; [d]Paclitaxel + Trastuzumab; [e] Docetaxel + Carboplatin + Trastuzumab; [f]Paclitaxel + Trastuzuman→ Fluoro-uracil + Epirubicin + Cyclophosphamide; [g]Pertuzumab + Trastuzumab + Docetaxel

The most commonly used regimen was Paclitaxel + Trastuzumab (43%). The benefit of Her2 blockade has been shown in different landmark trials including Hera, Neosphere, Tryphaena and NEOALLTO trials. Further studies are being done investigating the role of Trastuzumab in Neoadjuvant chemotherapy. Event-free survival advantage and increase pCR are consistently documented in these studies. However, not all Her2 patients are given Her2 blockade. One of the possible reasons is the financial burden associated with targeted treatments in general.

Surgical Management

All patients underwent surgical management post neoadjuvant chemotherapy. None of the patients opted for Breast conservation surgery. Modified Radical Mastectomy was done with full axillary lymph node evaluation and dissection (Table 6).

Surgical Treatment	N=259	%
BCS[h]	0	0
MRM[i]	259	100
Axillary evaluation	259	

Table 6. Surgical Management after Neoadjuvant Chemotherapy.

[h]Breast Conservation Surgery; [i]Modified Radical Mastectomy; [e]ALND, Axillary Lymph node dissection

One of the goals of Neoadjuvant chemotherapy is to allow and improve Breast conservation rates if the woman desires it. Although breast conservation surgery is available as one of the surgical treatment options, modified radical mastectomy is still the widely accepted surgical treatment.

Pathologic complete response and other Pathologic features

pCR as a prognostic marker of long-term outcome is well-established translated to improve survival outcomes among TNBC and Her2 positive tumors [16]. The pCR, defined as absence of invasive

residual cancer in the breast and axillary lymph nodes, with or without ductal carcinoma-in-situ (DCIS) was seen in 46 patients (18%). Among the patients who achieved pCR, the most common subtype is Luminal/HER2 negative at 17% and the most common regimen used was Docetaxel followed by FEC (5FU+EC) at 39%. Among our patients who underwent Ki67 testing 13 patients (18%) achieved pCr, two of them with Ki67 <20.

The National Cancer Database was queried for breast cancer patients who received neoadjuvant chemotherapy. In this study, 13, 939 patients, pCR was achieved in 19% of all patients and was highest in Non-luminal, Her2 positive patients [17]. Our local data shows that using the standard regimens for neoadjuvant treatment, pCR can be at par with national data.

In a study by Liu et al [18], Lymphovascular invasion was noted to be associated with worse clinical outcome in breast cancer receiving Neoadjuvant chemotherapy in terms of DFS (HR 3.76 95% CI 2.07-6.83, p <0.01) an OS (HR 5.70 95% CI 2.08-15.64, p<0.01). Likewise, tumor necrosis is also an independent predictor for early recurrence and death from breast cancer (P<0.001) [19]. Lymphovascular invasion and tumor necrosis were positive in 10% and 20% of patients, respectively (Table 7).

Pathologic Features	N=259	%
Lymphovascular invasion		
Negative	217	84
Positive	27	10
Equivocal/Probable	15	6
Tumor necrosis		
Negative	208	80
Positive	51	20
Tumor infiltrating lymphocytes		
Negative	247	95
Positive	12	5

Table 7. Pathologic Features after Surgical Treatment.

Breast cancer has not previously been considered a highly immunogenic cancer. Observations of tumour- infiltrating lymphocytes (TILs) in and around neoplastic cells in tumour samples, and associations with improved pathological complete response and clinical survival end points notably in triple negative and HER2 positive breast cancer subtypes led to further investigations of TILs in breast cancer [20]. The PANACEA trial exploratory analysis showed that stromal TILs expression as low as ≥ 5% can predict a response rate to immune checkpoint inhibitor. Although reporting of TILs is still not standard in our institution, about 5% of patients were reported to have positive TILs.

In conclusion, among 259 patients, pCR is achieved in 18% of patients using standard chemotherapy. This study shows that the most common neoadjuvant regimen used was sequential Anthracycline and Taxane and most common subtype is Luminal/Her negative.

The results of this study show our local experience in the real world, using the best available neoadjuvant treatment for our patients. The goal is to pave the way for a more vigilant, aggressive and personalized treatment, the formulation of institutional neoadjuvant protocols with the main goal of improving response rates and survival.

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