



# Neoadjuvant Chemotherapy as a Model of Care: Optimizing Treatment of Mexican Breast Cancer Patients

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## Abstract

Neoadjuvant Chemotherapy (NACT) is the standard of care for locally advanced breast tumors and may be administered in some operable tumors, although its use has not been widely adopted in all settings. In Mexico, 52% of breast cancer patients receive NACT [1]. Many factors contribute to less use of NACT when compared to other countries, including the lack of assessment and treatment decision-making by a Multidisciplinary Team (MDT), unavailability of NACT therapeutics, and readiness of a complete histopathological report.

The aim of this review is to describe prognostic factors and provide evidence-based recommendations for both the optimal use of NACT and collaborative treatment decision making in our local setting to improve patient outcomes.

**Keywords:** Breast cancer; LABC; Neoadjuvant chemotherapy; Multidisciplinary teams

## National Epidemiology of Breast Cancer

In Mexico, Breast Cancer (BC) ranks first in incidence and mortality due to cancer in women. The states with the highest reported mortality due to BC are Coahuila (24.2), Sonora (22.6), and Nuevo León (22.4) [2,3]. Despite local efforts to collect disease data, there is not enough nor accurate data on BC incidence, prevalence and distribution across the country.

Over 56% of new cases are diagnosed as Locally Advanced Disease (LABC) [1,4]. The relative high rate of LABC may reflect the lack of disease awareness, absence of a comprehensive screening program, and established coordination among different levels of health care. These limitations to high quality care lead to delays in diagnosis and treatment [4,5]. Now more than ever, the increasing amount of information on tumor heterogeneity, global advances in innovative treatments and growing BC incidence, prompt for a better disease understanding along with multidisciplinary

treatment decisions to achieve better outcomes.

## Neoadjuvant Chemotherapy as a Model of Care in Early Breast Cancer

Historically, NACT was indicated solely for inflammatory or inoperable tumors. As new evidence of its benefits has become available, its use has been expanded. NACT's primary objective has evolved into the opportunity to increase the chance of conservative surgery (including the breast and axilla), evaluate *in vivo* sensitivity to systemic treatment, identify subgroup of patients with better outcomes based on the pathological response (pCR *vs.* non-pCR), as well as to adapt post-neoadjuvant treatment if residual disease is present [6].

Currently the indication of NACT according to international guidelines includes tumors from stage II and up (T2-T3, N0-N3) regardless of the histological subtype (less evidence for luminal A tumors and non-responder histology). The recommendation is based on studies that have shown the benefit in earlier stages [7-11].

The Pathological Complete Response (pCR) after NACT varies according to the BC subtype. Hormone Receptor (HR) positive tumors have a low response rate of approximately 15%. HER2-positive tumors pCR rate is 20% to 67%, and Triple Negative tumors (TN) approximately 40% to 50% [12]. A meta-analysis conducted between 1998-2006 including 6,625 patients from a total of 8 clinical German studies, reported that the highest rates of pCR were in young patients, with early stage disease, ductal histology, high grade, negative hormone receptors and HER2-positive tumors,  $p=0.0005$  [13].

HER2-positive tumors, when treated with NACT and trastuzumab, reach pCR rates ranging from 35% to 65%, while the use of HER2 dual blockade with pertuzumab increases pCR rate to 42% to 63% [7,11]. The TRYPHAENA trial evaluating neoadjuvant treatment with chemotherapy and dual anti-HER2 blockade, pCR rates up to 81% were achieved in patients with Estrogen Receptor (ER) - negative, HER2-positive tumors [7,11]. A meta-analysis that included 36 studies and 5,768 patients with HER2-positive disease showed a benefit in Disease-Free Survival (DFS) for patients with pCR compared to patients with residual disease, (HR 0.37; 95% CI 0.32 to 0.43); this association was even greater in patients with HR-negative disease (HR 0.29; 95% CI 0.24 to 0.36). The coefficient of determination  $R^2$  was significant for both DFS and Overall Survival (OS) with 0.63 and 0.29, respectively [14].

In a retrospective study conducted in Mexico evaluating HER2-positive BC patients, a median tumor size of 5.5 cm and 96% lymph node positive disease was detected. The pCR rate after NACT plus trastuzumab reached 49%. It also showed that patients who achieved a pCR had a significant increase in DFS and OS at 3 years compared to patients who did not reach pCR (88% *vs.* 83.1% and 98.1% *vs.* 92.3%, respectively). This study corroborates the benefit of reaching pCR similar to those reported in non-Mexican patients, even with a high tumor burden [15].

In triple negative tumors, pCR rates ranges from 20% to 34%; however, tumors demonstrating a basal subtype reach higher pCR rates of up to 45% to 56% [16]. On the other hand, with the use of platinum agents in BCRA1 mutated tumors, pCR rate can be as high as 83% [17]. It has been consistently demonstrated that in triple negative tumors, as with HER2 positive tumors, pCR is an important prognostic marker. The presence of residual disease increases the risk

of recurrence (HR 6.02, CI 95% 3.92 to 9.25) and death (HR 12.41, CI 95% 5.82 to 26.49) [16,17].

## Benefit of Neoadjuvant Chemotherapy in the Surgical Management

The use of NACT has increased the conservative surgery rate as up to 19% compared to the baseline surgical plan for operable BC cases and up to 27% in HER2-positive patients [11,18].

In patients in whom Axillary Lymph node Dissection (ALD) is performed, pathological examination reveals that only 40% have axillary metastasis at the time of surgery, which means that up to 60% of patients do not receive any additional benefit from this procedure. Performance of ALD is associated with multiple comorbidities that increase disease burden, including lymphedema, pain, risk of vascular or nerve injury, and shoulder weakness [19].

In LABC and positive lymph nodes patients, NACT has achieved a complete lymph node response in 40% of cases; however, this rate could vary according to BC subtype. The ACOSOG Z1071 trial showed that lymph node response rate was 21.1% in HR-positive/HER2-positive disease, 47% in HR-negative/HER2-positive, and 49.4% in triple negative tumors.

Recently, three different multicentric, international trials demonstrated the efficacy of sentinel node testing post NACT; an identification rate of about 90% to 94% was achieved, with a false negative rate of 12% [20-22]. These trials concluded that the identification of at least 3 nodes with double technique is needed in order to maintain the efficacy of SLN. More recent studies are evaluating the possibility of eliminating the use of ALD in patients with negative SLN after NACT, with the objective of avoiding an unnecessary procedure and its potential complications.

## Assessment of Pathological Response after Neoadjuvant Chemotherapy

An additional challenge for an accurate diagnosis and treatment evaluation is the evaluation of response after systemic treatment. One of the main problems relies on the proper assessment and definition of pCR. So far, at least 6 classifications have been described; the main differences are that some consider the presence of ductal *in situ* carcinoma, microinvasive disease and/or axillary metastatic lymph nodes.

The current recommendation is to recognize the absence of disease in the breast and axilla as a pCR. However, in Mexico, the lack of standardized reports leads to the inclusion of different definitions, further challenging the need to have standardized histopathological interpretation and reporting.

## Pathological Response after NACT as a Marker of Long-Term Benefit and Determinant of Adjuvant Treatment

According to previous findings, reaching a pCR has become an important objective to be assessed; it has been associated with increased DFS and OS. The first trial that showed the impact of the pCR on survival was the NSABP B18, which compared neoadjuvant *vs.* adjuvant chemotherapy. The initial results showed that DFS and OS rates were the same in both treatment groups [23]. In a long-term follow-up, it was shown that the subgroups with greater benefit were composed of women under 50 years of age at diagnosis, and those with pCR achieved an OS of 85% compared with 73% in the group

**Table 1:** Conclusions and recommendations.

Potential intervention areas	Description	Expected results
<b>Pathology</b>		
Evaluation of Estrogen Receptor/Progesterone Receptor/HER2	Standardization of how it should be measured, quality control, sample control, adequate IHQ report	Reduction in rates of false positive and false negative results, subtype incidence as expected, reduced overtreatment
Standardize the pathology report (minimum necessary information)	All pathology reports must contain a minimum of information that allows the physicians treatment selection	Adequate patient selection, reduction in overtreatment or under treatment
Quality reviews and standardization to reduce the mismatch among pathology laboratories	The pathology labs must be submitted to periodic procedure reviews	It could allow a reduction in low quality diagnosis from non-standardized laboratories
Creation of a quality control unit, dependent on Health Authority, to evaluate pathology laboratories quality control.	Control unit integrated by certified pathologist	Promotes a quality service from pathology labs in order to keep up with controls
Include in the quality evaluation report for breast cancer care centers, the criteria for a adequate pathology report and IHQ evaluation	To design a more strict evaluation an certification report for breast cancer units	Only centers with the necessary infrastructure for diagnosis and treatment will handle breast cancer patients
<b>Neoadjuvant Systemic Treatment</b>		
Improve the selection of patients candidates for NAC	Recommend the use of neoadjuvant therapy for triple negative tumors and HER2+ in patients with clinical and biological high risk tumors (larger than 2 cm with or without clinically positive axillary lymph nodes)	Less invasive surgery, increased rates of pCR, adequate selection of adjuvant treatment, better long term outcomes
	Continue the indication of neoadjuvant chemotherapy in locally advanced and inoperable tumors (inflammatory, tumors greater than 5 cm with infiltration to the skin or chest wall or both or lymph node conglomerates)	Increase the use of MD selection of treatment, patient centered, it would allow more conversion rates to operable tumors
<b>Multidisciplinary Management and Physician-Patient Education</b>		
Establishment of MDTs for the diagnosis and treatment of breast cancer	Educate about the importance of team work, facilitate the reunion between health care professionals	Selection of the most adequate treatment for the patient, avoid unnecessary treatment, increase the use of NAC, improve communication between treating physicians, reduce treatment delays, improve patient navigation
Make MDT as a part of the evaluation report for BC centers	Include as a part of the accreditation of the BC centers that MDT must be implemented in order to improve treatment decision	MDT as a must for BC centers to allow better treatment selection
In the private sector, encourage that the reimbursement/direct payment of the procedures should be based on the decision by a MDT	Sensibilization to de insurance companies to demand adequate treatment selection by certified physicians with a MDT schema	Disminution in treatment costs, avoid double treatment, ensure treatment by certified professionals
Select health care professionals involved in BC treatment: educate and increase sensibilization in accurate and timely diagnosis and adequate treatment	Promote continuous medical education for specialists as well as for primary care physicians and patients, with a primary focus on timely diagnosis, better therapeutic decision based on biopsy with histological information and phenotype by immunohistochemistry, where a balance between initial surgery and NAC is considered	It would allow shorter treatment times, reduces costs and improves patient management by ensuring the adequate health care professional
Eliminate the barriers to achieve peers communication with available technology	Use electronic platforms that favor communication with the third level of care and primary care physicians that facilitate diagnostic/therapeutic decision making	Decrease reunion costs and improve communication to achieve treatment decisions
Give adequate guidelines about patient selection and choice of treatment in the official Mexican Health Plan	Incorporate these recommendations into national guidelines, the Colima consensus and the National Cancer Plan	To line up BC treatment for Mexican patient, accomplish the same opportunities for all of the patients
Promote continuous education of the patient with the support of NGOs	Increase the information delivered to the patient to empower them and make them an active character in the disease evolution	Accomplish a patient centered treatment

with no complete response (p=0.0008); the association continued when the analysis was adjusted to tumor size, nodal status, and age at diagnosis. The reduction in the risk of death was 50% (HR 0.50; CI 95% 0.32 to 0.78) [24].

A meta-analysis that included 12 international clinical trials and a total of 11,955 patients reported that tumor eradication both in breast and axilla (ypT0, ypN0 or ypT0/is, and pN0) is associated with better Recurrence-Free Survival (RFS), with a HR 0.44, CI 95% 0.39 to 0.51, and HR 0.48, CI 95% 0.43 to 0.53, respectively, as well as a better OS with a HR 0.36, CI 95% 0.30 to 0.44. Although the BC subtypes showing the greatest benefit were the triple negative and HR-negative/HER2-positive patients, there is a tendency to improvement in the HR-positive/HER2-positive group [6].

Currently, not only a pCR is considered as a marker of good prognosis, but also the degree of residual disease after NACT is a prognostic factor for disease recurrence. Symmans developed a grading system called Residual Cancer Burden (RCB) [25], which

is a continuous index that combines the pathological findings of the tumor (size and cellularity) and lymph node metastases (number and size), to predict DFS. The results are summarized in three groups. At 5 years, the risk of recurrence for class I (CPR) was 2.4%, meanwhile for class III (extensive residual disease) it was 53.6%. The residual disease also proved to be an independent prognostic factor from the hormone receptor status, the use of adjuvant hormone therapy or the clinical stage at diagnosis.

Finally, the pCR, in addition to its implications in prognosis, is now used to guide treatment decision-making, allowing the escalation or de-escalation of drugs [26].

Accordingly, a benefit given by the use of NACT is to lead adjuvant therapy according to the pathological response. There are already two trials in which treatment decisions are considered on the basis of the post-neoadjuvant residual tumor. In the CREATE-X trial on patients with HER2-negative early BC, it was demonstrated that the addition of adjuvant capecitabine reduces the risk of recurrence of patients

who do not achieve a pCR after receiving NACT with anthracyclines and taxanes. In addition, the KATHERINE trial designed to study adjuvant treatment with T-DM1 in patients with HER2-positive post-neoadjuvant residual disease reported a reduction in risk of recurrence compared to adjuvant trastuzumab [27,28]. These findings provide an example of how treatment adjusted to the response of NACT can improve the clinical outcome.

## Real World Data from Mexican Oncologist

We conducted a survey among 56 medical oncologists in México, of whom 57% work in both public and private practice and 43% only in public practice. The results showed that 58.9% agreed that in 80% of cases with stage II TNBC or HER2-positive BC they would choose to administer NACT, as well as in 89.2% of patients with stage III TNBC or HER2-positive BC.

When asked about the method to assess pCR, 35% answered they use RCB as the preferred method, 26.7% Miller and Payne, 26.7% AJCC and the rest chose other options. When asked about the importance of the evaluation of pCR, 48.2% answered it is a surrogate for OS, 30.3% recognized that it is necessary to guide adjuvant therapy, and 17.8% answered it is a surrogate for Progression-Free Survival (PFS).

Despite the robust evidence of its benefits and the broad acceptance between treating physicians in our country as reported on our survey, the neoadjuvant model of care is not widely implemented in our BC centers. Lack of use of NACT is influenced by a general lack of resources, including infrastructure, specialized personnel and medications themselves, yet in other cases it may be due to physician inflexibility to work as in MDTs.

## Conclusions and Recommendations

Neoadjuvant chemotherapy has proven advantageous in multiple aspects of care for BC patients. In many countries it is now a standard procedure for both inoperable and operable patients, allowing improving outcomes and reducing morbidity. In our country, standardization of NACT use is still a work in progress. It is necessary to implement measures to adopt this practice and establish this strategy as a marker of quality care for BC institutions. We include some recommendations we consider necessary to improve breast cancer care in our setting (Table 1).

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