Axillary Management of Stage II/III Breast Cancer in Patients Treated with Neoadjuvant Systemic Therapy: Results of CALGB 40601 (HER2-Positive) and CALGB 40603 (Triple-Negative)

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BACKGROUND: Management of the axilla in stage II/III breast cancer undergoing neoadjuvant systemic therapy (NST) is controversial. To understand current patterns of care, we collected axillary data from 2 NST trials: HER2-positive (Cancer and Leukemia Group B [CALGB] 40601) and triple-negative (CALGB 40603).

STUDY DESIGN: Axillary evaluation pre- and post-NST was per the treating surgeon and could include sentinel node biopsy. Post-NST, node-positive patients were recommended to undergo axillary lymph node dissection (ALND). We report pre-NST histopathologic nodal evaluation and post-NST axillary surgical procedures with correlation to clinical and pathologic nodal status.

RESULTS: Seven hundred and forty-two patients were treated, 704 had complete nodal data pre-NST and post-NST. Pre-NST, 422 (60%) of 704 patients underwent at least 1 procedure for axillary node evaluation (total of 468 procedures): fine needle aspiration (n = 234; 74% positive), core needle biopsy (n = 138; 72% positive), and sentinel node biopsy (n = 96; 33% positive). Pre-NST, 304 patients were considered node-positive. Post-NST, 304 of 704 patients (43%) underwent sentinel node biopsy; 44 were positive and 259 were negative (29 and 36 patients, respectively, had subsequent ALND). Three hundred and ninety-one (56%) patients went directly to post-NST ALND and 9 (1%) pre-NST node-positive patients had no post-NST axillary procedure. Post-NST, 170 (24%) of the 704 patients had residual axillary disease. Agreement between post-NST clinical and radiologic staging and post-NST histologic staging was strongest for node-negative (81%) and weaker for node-positive (N1 31%, N2 29%), with more than half of the clinically node-positive patients found to be pathologic negative ($p < 0.001$).

CONCLUSIONS: Our results suggest there is no widely accepted standard for axillary nodal evaluation pre-NST. Post-NST staging was highly concordant in patients with N0 disease, but poorly so in node-positive disease. Accurate methods are needed to identify post-NST patients without residual axillary disease to potentially spare ALND. (J Am Coll Surg 2017;224:688–694. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Abbreviations and Acronyms

ALND = axillary lymph node dissection
BCT = breast-conserving therapy
CALGB = Cancer and Leukemia Group B
CNB = core needle biopsy
FNA = fine needle aspiration
HER2+BC = human epidermal growth factor receptor-2-positive breast cancer
L = lapatinib
NST = neoadjuvant systemic therapy
pCR = pathologic complete response
SNB = sentinel node biopsy
T = trastuzumab
TNBC = triple-negative breast cancer
wP = weekly paclitaxel

Neoadjuvant systemic therapy (NST) has been used to convert some patients with stage II to III breast cancer who were initially deemed to require a mastectomy to candidates for breast-conserving therapy (BCT) by downsizing the volume of disease.[1-4] Reducing the size of a breast tumor is often used to justify administration of systemic therapy in the neoadjuvant rather than the adjuvant setting, especially in patients with human epidermal growth factor receptor-2-positive breast cancer (HER2+BC) and triple-negative breast cancer (TNBC) for the need for adjuvant therapy is not in question. Importantly, BCT after NST has been found to have equivalent local, regional, and distant recurrence rates and overall survival compared with BCT performed before systemic adjuvant therapy.[1-4]

Although many NST trials have shown the ability of this approach to reduce the extent of breast surgery, data on the optimal approach and management of the axilla after NST are unclear. The presence or absence of axillary nodal metastases after NST remains an important prognostic factor for long-term outcomes. Although multiple studies[5-7] have demonstrated that NST can downstage node-positive axillae to node-negative in up to 40% of patients, the persistence of axillary nodal involvement after NST remains an important prognostic factor. However, the value of pre-NST confirmation of nodal involvement by fine needle aspiration (FNA) or core needle biopsy (CNB), the timing of sentinel node biopsy (SNB), and the role of axillary lymph node dissection (ALND) relative to clinical and pathologic nodal status before and after NST remain areas of controversy.

We sought to elucidate patterns of axillary management for patients with HER2+BC and TNBC enrolled in 2 large cooperative group prospective randomized trials. To address these questions, we incorporated identical practice-oriented surgical studies into 2 NST trials: Cancer and Leukemia Group B (CALGB) 40601, a randomized phase III trial that compared lapatinib (L) or the combination of L and trastuzumab (T) to T given in combination with weekly paclitaxel (wP) in HER2+BC; and CALGB 40603, a randomized phase II trial that tested the addition of carboplatin and bevacizumab to a standard neoadjuvant chemotherapy regimen of wP followed by dose-dense doxorubicin and cyclophosphamide in TNBC. The primary end point of these trials was pathologic complete response (pCR) and has been been published previously; CALGB 40601, which included 295 patients, demonstrated a 46% to 56% pCR rate in the breast, and 443 patients in 40603 had a 53% pCR rate in the breast.[8,9] For both studies, there was no study-mandated axillary management. For patients with node-positive disease either pre- or post-NST, level I/II ALND was recommended. We captured pre-NST percutaneous lymph node biopsy data, use/timing of SNB, and post-NST axillary management. This is a planned analysis of the combined trials with identical data acquisition to identify axillary practice patterns and assess the relationship between clinical and pathologic staging.

METHODS

Patient eligibility

Patients with stage II or III HER2+BC or TNBC patients with operable, biopsy-confirmed, previously untreated, non-inflammatory disease were eligible. For CALGB 40601, HER2 positivity was defined as immunohistochemical staining of 3+ or fluorescent in situ hybridization amplified (ratio $\geq$2.0) and for CALGB 40603 TNBC was defined as estrogen receptor and progesterone receptor expression $<$10%; and HER2 negativity was defined as immunohistochemical staining of 0 to 1+ or fluorescent in situ hybridization ratio of $<$2.0. The neoadjuvant systemic therapy regimens on both trials have been published previously.[8,9] The schematics are provided in Figures 1 and 2.

Study procedures

Baseline breast imaging, including mammography with or without focused breast ultrasound, was required for all patients. Magnetic resonance imaging was suggested but not mandatory as baseline imaging. In patients with clinically positive axillae, histologic confirmation was encouraged by FNA and/or CNB. Patients with clinically negative axillae at study entry could undergo a pre- or post-treatment SLN procedure or ALND after NST; in patients with a percutaneous positive axillae or