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Impact of Neoadjuvant Chemotherapy in Stage II–III Triple Negative Breast Cancer on Eligibility for Breast-conserving Surgery and Breast Conservation Rates:

Surgical Results From CALGB 40603 (Alliance)

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Abstract

Objective—To assess the efficacy of neoadjuvant systemic therapy (NST) at increasing the rate of successful breast-conserving therapy (BCT) in triple negative breast cancer.

Background—Inducing tumor regression to permit BCT is often cited to support administration of NST. To quantify this benefit, we conducted a surgical companion study to CALGB40603, a randomized phase II, 2×2 factorial trial of neoadjuvant paclitaxel ± carboplatin ± bevacizumab (B) followed by doxorubicin plus cyclophosphamide ± B in stage II–III triple negative breast cancer.

Methods—Before and after NST, treating surgeons evaluated BCT candidacy by clinico-radiographic criteria; surgery performed was at surgeon and patient discretion. We measured (1) conversion rates from BCT-ineligible to BCT-eligible, (2) surgical choices in BCT candidates, and (3) rates of successful BCT with tumor-free margins.

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Results—Four hundred four patients were assessable for surgical outcomes. Two hundred nineteen (54%) were BCT candidates before NST. One hundred ninety-seven (90%) remained BCT candidates after NST, of whom 138 (70%) chose BCT, which was successful in 130 (94%). Of 185 (46%) who were not BCT candidates before NST, 78 (42%) converted to candidates with NST. Of these, 53 (68%) chose BCT with a 91% (48/53) success rate. The overall BCT-eligibility rate rose from 54% to 68% (275/404) with NST. Addition of carboplatin, B, or both increased conversion rates.

Conclusions—This is the first study to document prospectively a 42% conversion rate from BCT-ineligible to BCT-eligible, resulting in a 14% absolute increase in BCT eligibility. BCT was successful in 93% of patients who opted for it, but 31% of BCT-eligible patients still chose mastectomy.

Keywords

breast-conserving therapy; mastectomy; neoadjuvant therapy; surgery; triple negative breast cancer

Triple negative breast cancer (TNBC) is characterized by absent or minimal expression of estrogen (ER) and progesterone receptor and human epidermal growth factor receptor 2 (HER2). TNBC accounts for 15% of invasive breast cancers diagnosed in the United States, and is more common in younger women, African Americans, Hispanics, and BRCA1 mutation carriers. To determine the biologic interaction of systemic agents with the disease, neoadjuvant systemic therapy (NST) has been employed with increasing frequency. With no currently approved targeted agents for TNBC, standard treatment for TNBC remains chemotherapy. Patients who do not respond to NST or progress may switch to alternative chemotherapy agents or proceed directly to local therapy. Breast-conserving therapy (BCT) after NST has been shown to have equivalent local-regional recurrence rates and survival as BCT performed before systemic adjuvant therapy, and is therefore a safe option for patients.^{1–3}

Approximately one-third of patients with stage II and III TNBC treated with NST with anthracycline and taxane achieve a pathologic complete response (pCR). In an attempt to improve the pCR rates, CALGB (Cancer and Leukemia Group B, now part of the Alliance for Clinical Trials in Oncology) 40603, a phase II 2 × 2 factorial trial, was designed to examine the impact of adding carboplatin and/or bevacizumab (B) to conventional NST in TNBC on clinical activity, measured by pCR and toxicity.⁵ A prospective correlative surgical study built into the trial required surgeons to determine BCT eligibility both before and after NST. The surgical substudy also examined actual local therapy practice patterns.

A major limitation of the NST studies that have shown an increase in BCT rates is that the data are determined in a post hoc analysis. Prospective determination by the treating breast surgical oncologist of BCT eligibility pre-NST and conversion of ineligible patients to BCT-eligible patients has not been previously well studied in the context of preoperative cytotoxic chemotherapy. Furthermore, if a patient is determined to be a BCT candidate, the ultimate surgical choice and its success rate have not been well studied. In CALGB 40603, we prospectively sought to determine the conversion rate from BCT ineligibility to eligibility

and the rate of successful BCT with tumor-free surgical margins in women with newly diagnosed TNBC treated with NST.

METHODS

Patient Eligibility

Patients with stage II and III TNBC with operable, biopsy-confirmed, previously untreated noninflammatory disease were eligible, where TNBC was defined as ER and progesterone receptor expression less than 0% and HER2 negativity as immunohistochemical staining of 0 to 1+ or fluorescence in situ hybridization ratio of less than 2.0. Each participant signed an IRB (Institutional Review Board)-approved, protocol-specific informed consent in accordance with federal and institutional guidelines.

Study Procedures

Baseline breast imaging including mammography with or without ultrasound was required for all patients. Magnetic resonance imaging (MRI) was suggested but not mandated as baseline imaging. On the basis of physical examination, native breast size, and radiologic imaging of the tumor, the treating breast surgeons assessed eligibility for BCT before treatment initiation and at the end of NST. Although there was no standardization of criteria for assessing BCT ineligibility, the most common reasons cited were: tumor too large, probable poor cosmetic outcome, diffuse suspicious microcalcifications, and multicentric disease. In patients with clinically positive axillae, histologic confirmation by fine needle aspiration or core biopsy was encouraged. Patients with clinically negative axillae could undergo pretreatment or post-treatment sentinel lymph node (SLN) procedure. Successful BCT was defined as no tumor on ink of a partial mastectomy specimen. Mastectomy could be performed as a local therapy option with or without reconstruction. Surgical therapy occurred 4 to 8 weeks after cycle 4 of doxorubicin plus cyclophosphamide (AC), and at least 6 weeks after the last dose of B. Axillary SLN and/or axillary lymph node dissection was required at time of definitive local therapy except in patients with negative SLN pretreatment. Genetic testing was not required in this study.

The treatment arms, which have been previously published, are shown in Supplemental Digital Content Figure 1, available at <http://links.lww.com/SLA/A823>.⁵ In brief, all patients received paclitaxel (P) once per week for 12 weeks followed by AC once every 2 weeks with myeloid growth factor support for 4 cycles. They were randomly assigned to receive P with or without concurrent carboplatin (Cb) once every 3 weeks for 4 cycles and independently to treatment with or without B every 2 weeks for 9 cycles during administration of P and the first 3 cycles of AC.

Pathologic response was determined locally, with pCR in the breast being defined as the absence of residual invasive disease with or without ductal carcinoma in situ (yp T0/is). pCR in the breast/axilla was defined as pCR in breast and absence of any tumor deposit more than 0.2 mm in sampled lymph nodes (ypT0/isN0)

Data Collection and Analysis

The primary variable of interest was conversion from pre-NST BCT ineligibility to post-NST eligibility. Eligibility for BCT (both pre- and post-NST) was scored as yes/no. The rate of conversion to BCT candidacy was calculated as the number of patients whose eligibility for BCT changed from pre- to post-NST assessment from ineligible to eligible divided by the number who were ineligible at pre-NST (see Supplemental Digital Content Tables, available at <http://links.lww.com/SLA/A824>). Additional items of interest were: (1) proportion of patients who were BCT candidates both before and after NST; (2) proportion of candidates who attempted BCT; (3) incidence of BCT success; and (4) final surgical procedure. Proportions and their respective 95% confidence intervals were calculated using exact binomial methods. Comparisons of proportions across groups (arms) were made with the χ^2 test.

Analyses used an intent-to-treat approach that included patients who began protocol-specified NST who were analyzed according to their randomized assignment.

Data were collected and stored at the CALGB (now Alliance) Statistics and Data Center. Data quality was ensured by data review by the Data Center, the study chairperson (W.S.), surgical co-chair (M.G.), and additional surgical expert (D.W.O.). Analyses were performed by CALGB statisticians using SAS 9.2 (SAS Institute, Cary, NC). The data cutoff for this report was January 2015.

RESULTS

Between July 2009 and August 2012, CALGB 40603 enrolled 454 patients, of whom 443 began protocol treatment. Results of the primary treatment study were previously published.⁵ The addition of Cb and/or B to weekly P increased the incidence of pCR in the breast; specifically, 60% of patients who received Cb achieved pCR in the breast compared with 46% who did not. The B-containing arms had a combined pCR rate of 59% compared with 48% in the no-B arms. The arm that included both Cb and B had the highest pCR rate (67%).

Among the enrolled patients, 404 had complete surgical data and comprise the current study (see CONSORT diagram for details; see Supplemental Digital Content Figure 1, available at <http://links.lww.com/SLA/A823>). This subset was representative of the overall treatment study population. The majority of patients were between 40 and 59 years old with a median age of 49, 68% had clinical stage II disease, and 32% had clinical stage III disease (Table 1). High-grade disease was present in 77%; 90% of tumors were invasive ductal subtype and 55% of women were premenopausal.

Surgical Endpoints

Before NST, 54% (219) of patients were considered BCT candidates, of whom 197 (90%) remained candidates at post-NST assessment. Of the 46% (185) who were not BCT candidates before NST, 78 (42%) converted to candidates at post-NST assessment. In total, 68% of patients were candidates for BCT after NST. Among all post-NST BCT candidates, 69% (191) chose BCT, with an overall success rate of 93% (Table 2).

The proportion of patients who underwent BCT was similar for those who maintained BCT candidacy from pre- to post-NST evaluation compared to those who converted to candidates after NST treatment (70%–68%). Additionally, the BCT success rate was similar for the initial candidates and converted candidates who underwent BCT (94%–91%). Despite being BCT-eligible at post-NST evaluation, 30% of initial BCT candidates and 32% of the converted candidates underwent mastectomy. Overall, we prospectively quantified (1) a 42% conversion rate from BCT ineligibility to BCT eligibility in TNBC and (2) an overall 93% success rate for those who chose this approach. (Table 2) Despite these findings overall only 47% (191) of our patients underwent BCT, whereas 53% (213) underwent mastectomy (Table 3).

Correlation between surgical assessment of BCT candidacy and achievement of pCR is reported in Table 4. The percentage of patients found to have a pCR at surgery was nearly identical between those who were considered BCT-eligible at baseline and after NST (60%) and those who were initially scored BCT-ineligible but reclassified as BCT-eligible after treatment (58%). Among the small number of patients who were considered BCT-eligible pre-NST but were reclassified as BCT-ineligible after treatment, the pCR rate was 50%. We reviewed the reasons why these 22 patients became BCT-ineligible after NST; the most common reasons were the surgeon felt that the patient was at high risk of recurrence (with or without BRCA mutation) $n = 7$ and tumor too large in $n = 4$. Although patients who were classified as BCT-ineligible both before and after NST had the lowest pCR rate, 41% of this group achieved a pCR.

Results by Study Arm

BCT eligibility was not used as a stratification variable; as a result, the percentage of patients deemed BCT-ineligible at baseline assigned to the different treatment arms varied from 37% to 55% (46% for the overall study population) (Table 3). After NST, the percentage of patients deemed BCT candidates and the percentage that underwent BCT versus mastectomy differed little between treatment arms. However, compared with a 33% rate of conversion from BCT-ineligible to BCT-eligible for the control regimen, the conversion rate increased with the addition of B to 38%, with the addition of Cb to 45%, and with the addition of both B and Cb to 50%. The study was not designed to determine statistical significance for this endpoint.

DISCUSSION

The primary objective of CALGB 40603 was to determine whether adding Cb and/or B to standard NST in TNBC improved the pCR rate. Results indicated that the addition of Cb and/or B increased the pCR rate; it is too early to evaluate the effect on recurrence-free and overall survival.⁵ A prospective surgical substudy was embedded in the trial with BCT as the primary surgical endpoint. Surgeons were required to prospectively determine whether or not an individual patient was a BCT candidate before NST and then again after NST. As novel agents used in combination with standard NST continue to improve pCR rates, the question remains whether there is a concomitant increase in BCT rates? Like others, we

have shown an increase in BCT eligibility after NST and a high likelihood of success for those who choose BCT.

We have shown that 42% of patients who were initially deemed ineligible were converted by NST to BCT-eligible. In the study overall, 191 (47%) of patients underwent BCT, and 53 (28%) of them were conversions. More importantly, from a baseline BCT eligibility of 219 (54%), after NST 275 (68%) were eligible for BCT; the net increment of 56 patients is 14% of the total with a success rate of 93%. BCT success rate was similar whether a patient remained BCT-eligible (94%) or was converted to BCT-eligible (91%). The conversion rate was not statistically different across the arms, although it did track with the pCR rates. Compared with single-agent P (Arm 1), the addition of Cb and B (Arm 4) had the highest conversion rate to BCT eligibility (from 33% to 50%), although this difference was not statistically significant.

NST requires close coordination with the various disciplines of medical oncology, surgery, radiation oncology, breast imaging and reconstruction.⁶ Previous randomized trials from National Surgical Adjuvant Breast and Bowel Project (NSABP) and European Organization for Research and Treatment of Cancer on NST used standard adjuvant therapy as the comparator; those trials have shown similar survival and local-regional control between adjuvant and NST approaches. They have also shown increased rates of BCT when the trials compared systemic therapy before and after surgery.¹⁻³ NSABP B18 increased BCT from 60% to 68% when systemic therapy was given before surgery. The addition of docetaxel in NSABP B27 was also associated with a statistically nonsignificant increase in BCT rate from 61% to 63%. Trials from the Royal Marsden and Institute Curie also showed numeric increase in BCT rates of 78% to 89% and 77% to 82% when systemic therapy was given first.^{7,8} With development of novel therapeutic agents, NST has increased pCR rates over time.

It might be expected that an increase in pCR rates would lead to an increase in the number of patients who undergo BCT; however, this has not always been the case. The report from NeoALTTO by Criscitiello et al, a trial that assessed the use of anti-HER2 therapy in the neoadjuvant setting, showed that pretreatment characteristics and not pCR were the major factors associated with the type of surgery.⁹ In fact, the striking increase in pCR rate (absolute difference of 20%) with the use of dual HER2 blockade compared to single agent therapy did not improve BCT rates. They showed that the planned surgery at the initiation of NST, multicentricity, ER status, tumor size, and presence of residual tumor on palpation were determinants of the type of surgery received after NST. NeoALTTO did not require surgical reassessment after NST, which was a mandatory requirement of CALGB 40603. In GeparSixto, von Minckwitz et al showed that the addition of Cb to standard chemotherapy in TNBC increased pCR rates from 37% to 53%; however, there was no significant change in the HER2-positive group. Interestingly, their overall BCT rates were much higher than those in our study, at 75.9% for standard chemotherapy and 72.1% with the addition of Cb; however like our study, the addition of Cb and concomitant increase in pCR did not improve BCT rates.¹⁰

The determination of BCT eligibility requires a thorough workup by the treating surgical oncologist, which includes physical examination and breast imaging before and at the conclusion of NST. Mammography is the standard of care for newly diagnosed patients with breast cancer with or without ultrasound. MRI is becoming increasingly used in newly diagnosed patients who will be treated with NST and has been shown to have the highest size correlation coefficient to pathologic tumor size compared with other imaging modalities; it also has been shown to detect additional abnormalities that lead to additional imaging and biopsy. In addition, MRI has been partially responsible for the increasing mastectomy rates seen in the United States.^{11,12} The CALBG 40603 protocol strongly recommended the use of breast MRI, which may partially explain the high mastectomy rates. A study of NCCN (National Comprehensive Cancer Network)-designated centers showed a trend in higher mastectomy rates in younger women even in the setting of a response on post-NST MRI, suggesting other factors besides response in surgical decision making.¹³ After NST, a thorough re-evaluation with physical examination and the same imaging modalities should be used to determine the local therapy option(s). A strength of our trial was the requirement that the surgeon determine BCT eligibility before and then again after NST.

Our study has limitations. First, genetic information was not required for this trial and a higher percentage of patients with BRCA-related malignancies opt for mastectomy or bilateral mastectomy and thus even if the surgeon deemed her to be a candidate on the basis of imaging and examination criteria, this may not have been the best approach for the patient.^{14,15} Next we did not study specific patient or surgeon factors such as fear of cancer recurrence, need for future imaging, or potential surgeon biases in the local therapy decision-making process.^{16–18}

CONCLUSIONS

In conclusion, this is the largest prospective study of NST for the treatment of women with TNBC to report findings related to BCT eligibility as determined both pre- and post-NST. Our results show that a patient can undergo BCT with a high likelihood of success, as defined by tumor-free margins, if she is deemed an appropriate candidate by her treating surgical oncologist on the basis of clinical and radiologic profile. If one of the purported benefits of NST is to improve BCT rates, then we as surgeons must take into consideration the high likelihood of success in patients deemed candidates for BCT. The multidisciplinary nature of NST requires close coordination with surgery, medical oncology, radiation oncology, and imaging that will hopefully lead to improved rates of breast conservation and patient-centered outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Demographics

Characteristic	N assessable	404
Stratification		
Clinical stage		
II	276 (68%)	
III	128 (32%)	
Baseline variables		
Patient age		
20–29	10 (2%)	
30–39	83 (21%)	
40–49	122 (30%)	
50–59	121 (30%)	
60–69	59 (15%)	
70–79	9 (2%)	
Median	49	
IQR	40–56	
Min, max	26–79	
Menopausal status		
Premenopausal	222 (55%)	
Postmenopausal	182 (45%)	
Tumoral ER status		
Negative	376 (93%)	
Positive	25 (6%)	
Missing	3 (1%)	
Tumoral PR status		
Negative	386 (96%)	
Positive	14 (3%)	
Missing	4 (1%)	
Tumor grade		
Low	7 (2%)	
Intermediate	45 (11%)	
High	310 (77%)	
Missing	42 (10%)	
Tumor histology		
Ductal	362 (90%)	
Lobular	3 (1%)	
Mixed ductal + lobular	16 (4%)	
Invasive, NOS	8 (2%)	
Other	11 (3%)	
Missing	4 (1%)	

IQR indicates interquartile range; NOS, not otherwise specified; PR, progesterone receptor.

TABLE 2

BCT Candidacy, Attempt, and Results

BCT Candidate Pre-NST (N = 404)	BCT Candidate Post-NST			
	No	Yes	If Yes, BCT Attempted?	If BCT Attempted, Successful?
Yes 219 (54%)	22 (10%)	197 (90%)	138 (70%)	130 (94%)
No 185 (46%)	107 (58%)	78 (42%)	53 (68%)	48 (91%)

TABLE 3

BCT Candidacy, Conversion, and Final Procedure

Category N	Total 404	Arm			
		1 = P 101	2 = P+B>B 100	3 = P+Cb 101	4 = P+Cb+B>B 102
BCT candidate pre-NST					
Yes	54%	55%	63%	53%	45%
	Remained BCT candidate post-NST				
	90%	84%	94%	93%	89%
	46%	45%	37%	47%	55%
No	Converted to BCT candidate post-NST				
	42%	33%	38%	45%	50%
BCT candidate post-NST regardless of pre-NST status					
Yes	68%	61%	73%	70%	68%
Final surgery					
BCT	47%	44%	49%	50%	46%
Mastectomy	53%	56%	51%	50%	54%

TABLE 4

pCR by BCT Candidacy

BCT Candidate		N	pCR in Breast % (95% CI)
Pre-NST	Post-NST		
Yes	Yes	197	60% (53%–66%)
Yes	No	22	50% (31%–69%)
No	Yes	78	58% (47%–68%)
No	No	107	41% (32%–51%)
Total		404	54% (49%–59%)

CI indicates confidence interval.