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Characterizing response to neoadjuvant chemotherapy in invasive lobular breast carcinoma

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ABSTRACT

Background: Pathological complete response (pCR) after neoadjuvant chemotherapy (NCT) for breast cancer is associated with improved survival and facilitates conservative surgical strategies. Invasive lobular carcinoma (ILC) has been observed to have decreased response to NCT compared with invasive ductal carcinoma (IDC). This study seeks to evaluate national trends in the use of NCT for ILC compared with IDC, and determine if there is a subset of ILC patients who demonstrate favorable response rates.

Methods: This is a study using the National Cancer Database. The cohort consisted of patients with stage 1-3 ILC treated between 2010 and 2014, and a reference cohort of patient with IDC. For patients receiving NCT, pCR was assessed and clinically relevant variables were used in multivariable logistic regression models for each histologic subtype, modeling for pCR achievement. Survival analysis was performed for each histologic group to evaluate potential survival benefits of achieving pCR.

Results: Our study cohort consisted of 384,887 women, of which 9.7% had ILC. A significantly lower rate of pCR after NCT was found in the cases of ILC compared with those of IDC (8.7% *versus* 23.2%). Increased response was seen in ILC patients with HER2-positive and TNBC subtypes. A survival benefit was demonstrated in patients with ILC who achieved pCR.

Conclusions: While response to NCT in patients with ILC is uncommon, our findings demonstrate a selective benefit for patients with HER2-positive tumors and TNBC. In addition, pCR is correlated with a clear survival advantage in ILC.

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Background

Along with the implementation of screening policies leading to earlier detection of breast cancer, improvements in systemic therapy have been vitally important as a determinant of increased patient survival. The use of neoadjuvant chemotherapy (NCT) has proven useful in facilitating breast conserving therapy and reducing the burden of axillary disease.[1-10] As a result, NCT has become more widely accepted as an option in the management of breast cancer.[1-6] Achievement of pathological complete response (pCR), defined by the U.S. Food and Drug Administration as noninvasive or *in situ* cancer residuals in the breast and all sampled lymph nodes, after NCT has been correlated with improved outcomes.[6] pCR can be used as a surrogate indicator of overall survival, allowing for the assessment of tumor response to NCT and the discrimination between favorable and unfavorable outcomes in certain subsets of patients.[11,12] However, response to NCT varies significantly between different breast cancer subtypes. Patients with invasive lobular carcinoma (ILC), accounting for approximately 15% of all cases of breast cancers in the United States, have been shown to have lower response rates to NCT when compared with patients with invasive ductal carcinoma (IDC), the most frequent histologic subtype.[13] Studies have reported pCR rates ranging from 3% to 11% in ILC patients treated with NCT, compared with 16.7%-25% in IDC patients.[5,6,14-16] As a result of the tendency for lower pCR rates in patients with ILC, NCT is used less frequently in these patients on a national level, which could impact their ability to derive the benefits of NCT.[16-18] However, our understanding of the importance of molecular subtypes in predicting the behavior of breast cancer suggests that intrinsic subtype classification, rather than histology, may be the primary driver influencing response to NCT. Consequently, there is a need to determine if a subset of patients with ILC demonstrating greater response to NCT can be identified based on distinctive tumor-specific characteristics.[19-23]

The purpose of this study is to characterize the overall utilization of NCT for ILC, determine the response to NCT in ILC, and identify characteristics that potentially predict improved pCR rates in ILC patients. As a secondary aim, we seek to determine if there is a 5-y survival benefit for patients with ILC who achieve pCR. Determining characteristics that differentiate patients with ILC who may benefit from NCT will help to inform clinical practice, leading to increased options and more effective treatment regimens for ILC.

Methods

Data source

The data used in this study were derived from deidentified National Cancer Database (NCDB) participant user files.[24,25] The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB compiles more than 34 million historical records from more than 1500 Commission on Cancer–accredited facilities and contains information from over 70% of newly diagnosed cancer cases in the United States. The study was submitted for IRB approval and received an exemption.

Cohort selection

The cohort for this study consisted of female patients in the NCDB with clinical stage 1-3 primary ILC diagnosed and treated between 2010 and 2014 at NCDB reporting facilities ($n = 600{,}573$). A comparison group of patients with stage 1-3 IDC was used as a reference cohort. We included patients treated in any NCDB facility type across all geographical regions of the United States. The analysis included patients who received only NCT. Patients were assessed for eligibility based on our exclusion criteria, which included multiple cancer sites, use of neoadjuvant endocrine therapy, and unavailability of key variables such as timing of systemic therapy, tumor marker testing, tumor grade, or surgical intervention description (See Fig. 1).

Statistical analysis

Statistical analysis was performed with SAS Version 9.4 (SAS Institute Inc, Cary, North Carolina). Descriptive statistics were used to describe the study cohort. Age was used as a continuous variable for initial cohort description, using *t*-tests for comparisons between groups; furthermore, age groups were created for categorical analyses. χ^2 tests were used to compare categorical demographic data, tumor characteristics, and systemic therapy regimens. Patients who received only NCT were then identified and similar descriptive statistics were used to analyze their characteristics. These patients were also assessed for their rates of pCR according to distinct demographic and tumor characteristics. Unadjusted logistic regression analyses were performed, modeling for independent association with the occurrence of pCR. Variables including age, ethnicity, comorbidity index, clinical TNM stage, tumor grade, and molecular subtype were selected for their clinical significance. These variables were then evaluated using multivariable logistic regression models, modeling for the occurrence of pCR. From these multivariable regression models, we obtained odds ratios and 95% confidence intervals (CIs) for each variable as a correlate of pCR.

The Kaplan–Meier method was used to estimate survival distributions, and logrank tests were used to assess the differences in overall 5-y survival, comparing between patients who achieved pCR and those who did not. The landmark method was applied using the time of the first surgical procedure as the time origin for the survival analysis, this being the point at which pCR can be determined based on surgical pathology reports. Cox proportional hazards regression models were fit to obtain adjusted hazard ratios for pCR, age group, ethnicity, comorbidity index, clinical stage, tumor grade, and molecular subtypes. The use of adjuvant hormonal therapy or postmastectomy radiation therapy was also included in the adjusted survival model.

Results

Based on the pre-established inclusion and exclusion criteria, our study cohort consisted of 36,785 (9.6%) women diagnosed