Does the time from diagnostic biopsy to neoadjuvant chemotherapy affect the rate of pathologic complete response in stages I–III breast cancer?

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ABSTRACT

Background  Studies in the adjuvant setting suggest that the timing of breast cancer diagnosis, surgery, and chemotherapy might affect outcomes. In the neoadjuvant setting, data exploring whether expeditious neoadjuvant chemotherapy (NAC) after diagnosis improves the rate of pathologic complete response (pCR) in breast cancer are limited.

Methods  Patients who received NAC and completed treatment between May 2012 and December 2018 were identified from a prospectively collected database at BC Cancer. Time from diagnosis to start of NAC was calculated. Patients were grouped into those who did and did not experience a pCR, and those who started NAC within 28 days or after 28 days [time to NAC (TTN)]. The association between pCR and TTN was tested using logistic regression.

Results  In the time period studied, 482 patients who received NAC were identified. After exclusions, 421 patients met the eligibility criteria. Median time from biopsy to chemotherapy was 33 days (range: 7–140 days). In 149 patients (35.4%), NAC was received within 28 days of diagnosis (range: 7–28 days); in 272 patients (64.6%), it was received after more than 28 days (range: 29–140 days). The overall pCR rate was 31.8%. A trend toward a higher pCR rate, although not statistically significant, was observed in the group that initiated chemotherapy within 28 days (34.2% vs. 30.5%, p = 0.43). In the logistic regression model, rates of pCR were associated with receptor status, but not age, stage, or TTN.

Conclusions  In the neoadjuvant setting, we observed no difference in the rate of pCR in patients who started NAC within 28 days or after 28 days.

Key Words  Breast cancer, neoadjuvant chemotherapy, pathologic complete response, time to treatment

BACKGROUND

Use of the neoadjuvant approach to treat breast cancer (BCa) has been increasing since the early 2000s. Several studies have demonstrated similar outcomes when chemotherapy is given before compared with after BCa surgery. Neoadjuvant treatment has several advantages, such as rendering inoperable BCa operable, improving surgical options for enhanced breast-conserving surgery (BCS), and providing an assessment of a tumour’s response to systemic treatment. Neoadjuvant treatment also has prognostic implications, because pathologic complete response (pCR) has been shown to be a good prognostic marker for the effectiveness of neoadjuvant chemotherapy (NAC) and is a validated surrogate endpoint for disease-free survival and overall survival. A recent patient-level meta-analysis presented at the 2018 San Antonio Breast Cancer Symposium demonstrated significantly improved disease-free survival and overall survival outcomes in patients who achieve a pCR compared with those who do not after NAC.

Although the advantages of neoadjuvant treatment in BCa have been well established, the optimal time intervals between interventions in the neoadjuvant setting are not known. In contrast, many studies in the adjuvant setting have explored optimal time intervals from surgery to the initiation of systemic therapy. Studies have shown that
delaying adjuvant chemotherapy beyond 8–12 weeks after surgery is associated with inferior outcomes. The time from initial biopsy to surgery has also been studied and has been shown to be associated with BCA outcomes. A large population-based cohort study from Sweden looking at 7017 women who received surgery for BCA from 2001 to 2008 showed that the risk of death from all causes increased by 1.1% per day from BCA diagnosis to surgery (hazard ratio: 1.011; 95% confidence interval: 1.006 to 1.017). In terms of cancer-specific risk, a large U.S. Surveillance, Epidemiology, and End Results program database and National Cancer Database cohort study looked at 60-day intervals from diagnosis to surgery and observed that lower rates of disease-free survival and overall survival were associated with greater time intervals from diagnosis to surgery.

In the neoadjuvant setting, data to establish whether longer times from diagnosis to the initiation of NAC are associated with poorer outcomes are limited. We sought to determine whether initiation of NAC within 4 weeks of the biopsy date affects the likelihood of achieving a pCR, defined as absence of residual disease in both breast and axilla, for patients with biopsy-proven BCA.

METHODS

Study Design and Patient Selection

This prospective cohort study enrolled individuals who received neoadjuvant chemotherapy for BCA between May 2012 and December 2018 at BC Cancer in Vancouver. All patients with histologically proven BCA seen at BC Cancer for consideration of NAC have been prospectively captured in a secure quality assurance and improvement database since May 2012. A data quality review takes place every 4 months, and the most recent quality review, in July 2018, demonstrated 95.2% alignment. Patients who received at least 1 cycle of NAC and had definitive breast surgery were included in the study. Patients were excluded if they had bilateral BCA at the time of diagnosis or if their postoperative pathology reports were unavailable.

Potential prognostic and predictive factors—age; estrogen receptor, progesterone receptor, and HER2 receptor status (positive or negative) as determined institutionally, but aligned with guidelines from the American Society of Clinical Oncology and the College of American Pathologists; and clinical stage at diagnosis—were extracted from the database. Date of initial core biopsy confirming the BCA diagnosis and date of the first dose of NAC received were recorded. The time to NAC (TN) from diagnostic biopsy for each patient was then calculated in days. Patients were divided into two categorical groups for clinical relevance and ease of interpretation: those who received NAC within 28 days of the biopsy date (TN≤28) and those who started after 28 days (TN>28). In addition, the date of the last dose of NAC received and the date of definitive surgery were also recorded. The type of breast surgery performed (mastectomy or BCS) and the surgical procedure used in the axilla (axillary lymph node dissection or sentinel lymph node biopsy) were also extracted for each patient.

This study was approved by the Research Ethics Board of BC Cancer. No funding was provided to support the study.

Outcome Measures

The outcome of pCR was used because of its demonstrated value as a surrogate endpoint for survival. It was defined as the absence of invasive cancer in both breast and axilla at the time of surgery regardless of the presence or absence of in situ disease. The outcome of pCR was recorded as achieved or not achieved for all patients. The proportion of patients who achieved a pCR in each group was calculated and compared. Patients were further divided into subgroups based on receptor status and stage. The proportion of patients who achieved a pCR in each subgroup was determined.

Statistical Analysis

Baseline characteristics were compared descriptively for the two TN groups. To establish the statistical significance of the demographic differences between the TN groups, the 2-tailed t-test was used for age at diagnosis, and the chi-square test was used for clinical stage and receptor status. Median time to treatment for the whole cohort was determined and reported with 95% confidence intervals. The proportion of patients achieving a pCR was compared for the TN groups using the chi-square test. The same comparison was also carried out for each receptor status subgroup. Statistical significance was set at p < 0.05. A logistic regression analysis was performed with pCR as the dependent variable and age, stage, receptor status, and time to NAC (continuous) as the independent variables.

RESULTS

From May 2012 to December 2018, 482 patients who received NAC for histologically proven invasive BCA at BC Cancer were identified (Figure 1). Twelve patients with bilateral BCA were excluded. Of the remaining 470 patients with unilateral BCA, 43 did not proceed to surgery for reasons described in Figure 1, and 6 patients had incomplete charts. Thus 421 patients met the eligibility criteria and were included in this study.

Median time between biopsy and first dose of NAC for the overall cohort was 33 days (range: 7–140 days; Table 1). In the overall cohort, 149 patients (35.4%) were treated within 28 days of biopsy (range: 7–28 days), and 272 patients (64.6%) were treated after 28 days from biopsy (range: 29–140 days). Median age at diagnosis for the overall cohort was 51 years (range: 26–85 years). Patients with TN>28 had a median age at diagnosis of 53 years (range: 27–85 years); those with TN≤28 had a median age at diagnosis of 49 years (range: 26–79 years).

In terms of pretreatment clinical stage, 2.9% of all patients had stage I BCA, 56.0% had stage II disease, and the remaining 41.1% had stage III cancer. No statistically significant difference in stage distribution was evident for the patients with TN>28 and with TN≤28 (p = 0.10). The distribution of receptor statuses was different in the TN groups (p = 0.02), with more triple-negative BCA in the TN≤28 group than in the TN>28 group (33.6% vs. 19.9%) and less HER2-positive BCA in the TN≤28 group than in the TN>28 group (34.9% vs. 45.6%).

Median time from NAC to surgery was 34 days after the last dose of chemotherapy (range: 6–273 days). In terms of
type of surgery performed, 66.0% of patients had a mastectomy, and 31.2% had BCS. In the mastectomy group, 71.9% (200 of 278 patients) had axillary lymph node dissection, and 28.1% (78 of 278 patients) had sentinel lymph node biopsy. In the BCS group, 48.1% (63 of 131 patients) had axillary lymph node dissection, and 51.9% (68 of 131 patients) had sentinel lymph node biopsy. In the type-of-surgery groups, no difference was observed for patients in the \( t_{TN} \leq 28 \) and \( t_{TN} > 28 \) groups (\( p = 0.90 \)).

**pCR**

A logistic regression analysis explored the associations of various clinicopathologic and prognostic factors with pCR (Table II). Receptor status was associated with the rate of pCR, but age, stage, and \( t_{TN} \) were not. Further, no association of \( t_{TN} \) with pCR was observed in a logistic regression analysis based on receptor status subgroup.

Of all patients studied, 31.8% achieved a pCR (Table III). In the \( t_{TN} \leq 28 \) group, 34.2% of patients achieved a pCR; in the \( t_{TN} > 28 \) group, the percentage was 30.5%. However, that numeric difference was not statistically significant (\( p = 0.43 \)).

With respect to receptor subgroups, the overall pCR rate in patients with HER2-positive BCA was 48.3%, and a pCR was observed more frequently in patients with hormone receptor–negative, HER2-positive disease (57.5%). Patients with triple-negative BCA had a pCR rate of 33.7%, and patients with hormone receptor–negative, HER2-negative disease had a pCR rate of 11.0%. When grouped in terms of \( t_{TN} \leq 28 \) and \( t_{TN} > 28 \), no differences in pCR rates were observed based on receptor status (Table III). Likewise, pretreatment clinical stage did not seem to be associated with the overall pCR rate (stage I: 33.3%; stage II: 32.3%; stage III: 31.2%). When grouped by \( t_{TN} \leq 28 \) and \( t_{TN} > 28 \), pCR rates remained unaffected (stage I: \( p = 0.41 \); stage II: \( p = 0.88 \); stage III: \( p = 0.20 \)).

**DISCUSSION**

Our study provides evidence that urgently starting NAC after diagnostic biopsy is not significantly associated with pCR outcomes. Compared with patients who received NAC more than 4 weeks from diagnostic biopsy, those who received NAC within 4 weeks of diagnostic biopsy were not more likely to achieve a pCR. That observation was also evident in receptor status subgroups.

To our knowledge, only one other retrospective study, by Sebai et al., explored outcomes based on time intervals from diagnosis to NAC. That study looked at 720 patients in an institutional tumour registry database from 2003 to 2015 who underwent NAC, and the authors did not observe an association of overall survival with longer time from diagnosis to NAC. Given the paucity of data and lack of guidelines for optimal timing of NAC, and the fact that treatment strategies changed during the period of time studied by Sebai et al., our data are informative. In addition, achieving a pCR after neoadjuvant treatment in BCA is emerging as a factor influencing the decision for further adjuvant therapies, and thus an understanding of how the timing of NAC can influence pCR is critically important to being able to interpret adjuvant studies.

In the adjuvant setting, the relationship of outcomes with time to initiation of chemotherapy after surgery has been explored in a number of retrospective studies, with evidence of poorer outcomes in patients who start adjuvant chemotherapy later than 8–12 weeks after surgery. That relationship has also been studied in the various receptor...
status subgroups. Eastman et al.\textsuperscript{15} reported a trend toward worse survival in triple-negative breast cancer with adjuvant chemotherapy delays of more than 90 days ($p=0.06$). More recently, in 2018, a retrospective study presented at the San Antonio Breast Cancer Symposium looking at 687 patients with stages I–III triple-negative breast cancer receiving adjuvant chemotherapy from 2000 to 2014 demonstrated worse recurrence-free survival and overall survival when chemotherapy was given more than 30 days after surgery\textsuperscript{16}. Compared with patients who received chemotherapy before 30 days after surgery\textsuperscript{18}. Compared with patients who received chemotherapy before 30 days from surgery, those who received chemotherapy 31–60 days, 61–90 days, and 90 days or more from surgery had hazard ratios for survival of 1.94, 2.45, and 2.79 respectively. Given that large randomized controlled trials and meta-analyses have generally considered survival outcomes with adjuvant compared with neoadjuvant approaches to be similar, our data suggest that such a relationship might not be preserved when timing of NAC is considered in triple-negative breast cancer\textsuperscript{2–4}. Any cohort study design has inherent limitations. Although our study was conducted at a single institution, that institution is a large tertiary care centre, and the data come from a large adjudicated quality assurance program, allowing for robust and detailed patient-level data. Because this was an observational study, groups were not balanced, and differences in the TTN groups in terms of receptor status distribution were evident (Table I). In addition, the study did consider whether the amount of NAC received in the TTN groups differed, which could potentially influence the outcomes observed.

### TABLE I  Baseline characteristics of the study groups

| Characteristic | Time to NAC | p Value |
|---------------|-------------|---------|
|               | Overall     | ≤28 Days | >28 Days |
| Patients (n)  | 421         | 149      | 272      |
| Age at diagnosis (years) | | | |
| Median        | 51          | 49       | 53       |
| Range         | 26–85       | 26–79    | 27–85    |
| Clinical stage [n (%)] | | | |
| I             | 12 (2.9)    | 5 (3.4)  | 7 (2.6)  | 0.10 |
| II            | 236 (56.1)  | 73 (49.0)| 163 (59.9)| |
| III           | 173 (41.1)  | 71 (47.7)| 102 (37.5)| |
| Receptor status [n (%)] | | | |
| HR+, HER2+    | 85 (20.2)   | 25 (16.8)| 60 (22.1)| 0.02 |
| HR–, HER2–    | 91 (21.6)   | 27 (18.1)| 64 (23.5)| |
| HR+, HER2–    | 141 (33.5)  | 47 (31.5)| 94 (34.5)| |
| HR–, HER2–    | 104 (24.8)  | 50 (33.6)| 54 (19.9)| |
| Mastectomy\textsuperscript{a} [n (%)] | | | |
| ALND          | 200 (47.5)  | 75 (50.3)| 125 (46.0)| 0.90 |
| SLNB          | 78 (18.5)   | 25 (16.7)| 53 (18.5)| |
| Breast-conserving Sx\textsuperscript{b} [n (%)] | | | |
| ALND          | 63 (15.0)   | 21 (14.1)| 42 (15.4)| |
| SLNB          | 68 (16.2)   | 23 (15.4)| 45 (16.5)| |
| Biopsy date to first NAC dose (days) | | | |
| Median        | 33          | 23       | 38       |
| Range         | 7–140       | 7–28     | 29–140   |
| Last NAC dose to Sx date (days) | | | |
| Median        | 34          | 35       | 34       |
| Range         | 6–273       | 13–160   | 6–273    |

\textsuperscript{a} In 278 patients.
\textsuperscript{b} In 131 patients.

NAC = neoadjuvant chemotherapy; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy; Sx = surgery.

### TABLE II  Logistic regression model for associations of clinicopathologic and prognostic factors with pathologic complete response

| Parameter | OR  | 95% CI       | p Value\textsuperscript{a} |
|-----------|-----|--------------|-----------------------------|
| Age       | 1.004 | 0.99 to 1.02 | 0.68                        |
| Receptor status | | | |
| HR+, HER2+ | 5.32 | 2.71 to 10.45 | <0.01                       |
| HR–, HER2– | Reference | | Ref                     |
| HR+, HER2– | 11.00 | 5.59 to 21.63 | <0.01                       |
| HR–, HER2– | 4.11 | 2.07 to 8.13 | <0.01                       |
| Stage | | | |
| I       | Reference | | |
| II      | 0.95 | 0.26 to 3.44 | 0.94                        |
| III     | 0.99 | 0.27 to 3.65 | 0.99                        |
| Time to NAC | 1.00 | 0.99 to 1.02 | 0.87                        |

\textsuperscript{a} Significant values appear in boldface type.

OR = odds ratio; CI = confidence interval; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; NAC = neoadjuvant chemotherapy.
Ideally, a prospective trial looking at varying intervals between diagnostic biopsy and NAC would be informative, but challenging—if not impossible because of questionable ethics—to conduct. Despite those limitations, in an era of increasing health care demands and chemotherapy wait times, our study provides additional evidence that urgent NAC after diagnostic biopsy does not appear to be associated with pCR outcomes. That observation is important, given the many competing demands and pressures to begin cancer treatment as early as possible. In addition to increasing wait times, the prompt initiation of neoadjuvant treatment must also be balanced with the need to perform appropriate investigations before treatment (for example, bloodwork and staging imaging investigations). Such investigations are necessary to ensure that it is safe to proceed with neoadjuvant treatment and that patients with metastatic disease are not incorrectly treated with a neoadjuvant treatment paradigm that could result in overtreatment or in later ineligibility for standard-of-care first-line metastatic treatments or clinical trials.

Ultimately, the pressures to initiate NAC early come from many levels, including the physician, cancer care institution, and patient levels. The importance of the information gained from the present study and similar studies might help to alleviate some of the anxiety that patients experience by knowing that they could have more time to adjust to their diagnosis before starting neoadjuvant treatment.

CONCLUSIONS

Our study of 421 patients provides reassurance that NAC within 4 weeks of biopsy is not necessary to improve rates of pCR, regardless of receptor status. With pressures on health care professionals and the health care system as a whole to shorten wait times and do more with less, the present study highlights the importance of quality assurance and of studies to help identify the patient subgroups that could benefit from the prioritization of pressed resources.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare the following interests: DL reports a grant received from Pfizer for a trial in which he is principal investigator; CS reports honoraria received from Mylan, Sandoz, Lilly, Novartis, Roche, and Pfizer, and grants received from Pfizer, Roche, Merck, Lilly, Novartis, and Amgen. The remaining authors have no conflicts of interest to disclose.

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### TABLE III  Proportion of patients with a pathologic complete response (pCR) in each chemotherapy timing group

| Variable                          | Patient group | Overall pCR rate | Time to NAC [p (%)] | p Value | Continuation |
|-----------------------------------|---------------|------------------|---------------------|---------|--------------|
|                                   |               | Overall          | ≤28 Days (n=149)    | >28 Days (n=272) |
| Receptor status                   |               | Overall          | ≤28 Days (n=149)    | >28 Days (n=272) |
| HR+, HER2+                        | Overall       | 134 (31.8)       | 51 (34.2)           | 83 (30.5) | 0.43         |
| Achieved pCR                      | HR+, HER2+    | 89               | 25                  | 64       | 0.13         |
|                                   | HR+, HER2–    | 146              | 48                  | 98       | 0.33         |
| Achieved pCR                      | HR–, HER2+    | 16 (11.0)        | 7 (14.6)            | 9 (9.2)  | 0.33         |
| Achieved pCR                      | HR–, HER2–    | 50 (57.5)        | 14 (51.9)           | 36 (60.0) | 0.48         |
| Achieved pCR                      | Overall       | 33 (33.3)        | 17 (34.7)           | 16 (32)  | 0.78         |

Stage

| Variable | Stage | Overall | Achieved pCR |
|----------|-------|---------|--------------|
|          | I     | 12      | 4 (33.3)    |
|          | II    | 236     | 76 (32.2)   |
|          | III   | 173     | 54 (31.2)   |

| Variable | Stage | Overall | Achieved pCR |
|----------|-------|---------|--------------|
|          | I     | 5       | 1 (20.0)    |
|          | II    | 73      | 24 (32.9)   |
|          | III   | 71      | 26 (36.6)   |

| Variable | Stage | Overall | Achieved pCR |
|----------|-------|---------|--------------|
|          | I     | 7       | 3 (42.9)    |
|          | II    | 163     | 52 (31.9)   |
|          | III   | 102     | 28 (27.5)   |

NAC = neoadjuvant chemotherapy; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2.
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