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# Neoadjuvant Chemotherapy Is Associated with Improved Survival Compared with Adjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer Only after Complete Pathologic Response

**Carla S. Fisher, MD**[1], **Cynthia X. Ma, MD**[2], **William E. Gillanders, MD**[1], **Rebecca L. Aft, PhD**[1], **Timothy J. Eberlein, MD**[1], **Feng Gao, PhD**[3], and **Julie A. Margenthaler, MD**[1]

Julie A. Margenthaler: margenthalerj@wudosis.wustl.edu

[1]Department of Surgery, Washington University School of Medicine, St. Louis, MO

[2]Division of Oncology, Washington University School of Medicine, St. Louis, MO

[3]Division of Biostatistics, Washington University School of Medicine, St. Louis, MO

## Abstract

**Introduction—**Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer that is known to be chemosensitive. In patients with TNBC, we sought to compare survival outcomes between patients receiving neoadjuvant chemotherapy, with and without complete pathologic response (pCR), and those receiving adjuvant chemotherapy.

**Methods—**We performed a retrospective chart review and identified 385 patients with stage I–III TNBC who were treated with neoadjuvant or adjuvant chemotherapy between 2000 and 2008. Patients were divided according to receipt of neoadjuvant chemotherapy with pCR, neoadjuvant chemotherapy without pCR, and adjuvant chemotherapy. Data were compared using Fisher's exact test and analysis of variance (ANOVA). Kaplan–Meier curves were generated.

**Results—**Of 385 patients, 151 (39%) received neoadjuvant chemotherapy and 234 (61%) received adjuvant chemotherapy. Twenty-six (17%) of those patients receiving neoadjuvant chemotherapy had pCR. After controlling for covariates associated with survival in unadjusted tests, patients undergoing neoadjuvant chemotherapy with residual tumor had significantly worse survival compared with patients receiving adjuvant therapy [hazard ratio (HR) = 0.51, $P = 0.007$] and a trend towards worse survival compared with patients receiving neoadjuvant therapy with pCR (HR = 0.19, $P = 0.10$).

**Conclusions—**Although previous clinical trials have not demonstrated a survival difference between patients receiving neoadjuvant versus adjuvant chemotherapy for breast cancer, our study suggests an overall survival benefit in patients with pCR following neoadjuvant chemotherapy compared with patients receiving adjuvant therapy. It is clear that a prospective study needs to be carried out to better elucidate the timing of chemotherapy in patients with TNBC.

Breast cancer is the most common cancer among women in the USA, the second most common cause of cancer death, and the main cause of death in women aged 45–55 years. In 2009, approximately 192,370 American women were diagnosed with breast cancer, and an estimated 40,170 women died of the disease.[1]

Breast cancer is a known heterogeneous disease, and expression of estrogen receptor (ER), progesterone receptor (PR), and the oncogene ErbB-2/human epidermal growth factor receptor 2 (HER-2) are important markers in distinguishing breast cancer subtypes. Triple-negative breast cancers (TNBC) are characterized by lack of ER, PR, and HER-2

expression. They account for approximately 15% of breast cancers and tend to be histologically and clinically aggressive.[2,3] Despite their relative infrequency compared with other breast cancer subtypes, TNBC are of growing interest to clinicians for several reasons: they are associated with particularly poor outcomes including decreased disease-free (DFS) and overall survival (OS), there is no targeted therapy for TNBC, and TNBC has close associations with specific subgroups of women including premenopausal, African–American, and *BRCA* mutation carriers.[3–6]

In contrast to breast cancers expressing ER and HER-2 receptors with available directed therapy, options for treating TNBC have been limited, and chemotherapy is the standard method used to treat these patients. Interestingly, despite its poor prognosis, TNBC appears to be particularly chemosensitive when compared with the much more common ER+ cancers.[7] Additionally, this is demonstrated by a higher pathologic complete response (pCR) rate than for other subtypes of breast cancer when patients are treated with neoadjuvant chemotherapy.[6,8–12] pCR is not only encouraging following surgery but also predictive of future outcomes, as evidenced by studies demonstrating that patients who experience pCR following neoadjuvant chemotherapy have significantly better overall survival than those with residual disease. In addition, those TNBC patients who do not achieve pCR following neoadjuvant chemotherapy have a particularly poor outcome compared with non-TNBC.[6,13] These observations suggest that there is a subgroup of women with TNBC whose tumors are extremely sensitive to chemotherapy. What is not known is whether the timing of chemotherapy, either neoadjuvant or adjuvant administration, is more beneficial.

Despite its apparent chemosensitivity to neoadjuvant chemotherapy, no study has prospectively studied pre-operative versus postoperative chemotherapy in TNBC patients. Based on the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-18, the current dogma in therapy for breast cancer is that neoadjuvant and adjuvant chemotherapy are equivalent in terms of DFS and OS. That study, however, did not separate the various breast cancer subtypes when reporting outcomes. Based on studies showing different results with neoadjuvant chemotherapy in the various breast cancer subtypes, one must wonder whether the conclusions of the above study can be applied to TNBC in the same manner they are applied to other subtypes of breast cancer.

Based on these issues, we previously conducted a retrospective study of patients who underwent chemotherapy at our institution for TNBC, comparing preoperative and postoperative administration. After adjusting for factors found to significantly affect survival (tumor size, nodal positivity, and advanced stage), we demonstrated a survival benefit for women with TNBC who received adjuvant chemotherapy compared with those receiving neoadjuvant chemotherapy.[14] One limitation of our previous study was the lack of identification of patients with pCR versus those who had residual disease after neoadjuvant chemotherapy. In our current study, we address this limitation. Our primary aim was to identify any survival difference between the three groups and, secondarily, to identify any factors that could help predict pCR in patients undergoing neoadjuvant chemotherapy.

## METHODS

### Study Design

Institutional review board approval was obtained prior to commencement of this retrospective study. Written informed consent of patients was not required. The prospectively maintained surgical database was queried from January 1, 2000 to June 31, 2008 to identify all patients with a diagnosis of stage I–III biopsy-proven invasive TNBC who received neoadjuvant or adjuvant chemotherapy. Patients were divided according to

receipt of neoadjuvant chemotherapy, with and without pCR, or adjuvant chemotherapy, for analysis.

### Pathologic Assessment

Pathologic diagnosis, ER status, PR status, and HER-2/neu status were determined by standard immunohistochemical methods. Tumors with less than 1% stained cells were considered to have negative receptor status. HER-2/neu status was assessed by immunohistochemistry only if the results were 0 or 1+ staining and by fluorescence in situ hybridization (FISH) confirmation if 2+ immunohistochemistry staining was present. pCR was defined as absence of invasive breast cancer in the breast on final pathologic assessment; final pathologic nodal status was not considered in the definition of pCR versus non-pCR.

### Statistical Analyses

The primary outcome for this study was overall survival (OS), which was defined as the time from initiation of chemotherapy to date of death due to any cause. Survivors were censored at date of last contact. The distributions of patient and clinical characteristics across different chemotherapy groups were compared using Fisher's exact test or ANOVA as appropriate. The OS between different groups were estimated using Kaplan–Meier product-limit method and compared by log-rank test. A multivariate Cox proportional-hazard model was also fitted by a backward selection procedure to identify factors that were independently correlated with OS. All analyses were two-sided, and significance was set at *P*-value of 0.05. Statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC).

## RESULTS

During the study period from 2000 to 2008, we identified 385 patients with stage I–III TNBC who were treated with neoadjuvant or adjuvant chemotherapy. Patient and tumor characteristics are presented in Table 1. Of 385 patients, 151 (39%) received neoadjuvant chemotherapy and 234 (61%) received adjuvant chemotherapy. The chemotherapy regimens varied overall but did not differ between the three groups. The most common regimens in all groups were adriamycin and/or taxane based. Mean follow-up was 2.5 years and did not differ in the three groups.

Patients undergoing neoadjuvant chemotherapy were younger ($P < 0.05$) with larger tumor sizes and more advanced clinical stage than those undergoing adjuvant chemotherapy ($P < 0.0001$). The groups did not differ with regards to patient race, tumor histology, or tumor grade ($P > 0.05$).

Of the patients undergoing neoadjuvant chemotherapy, 26 (17%) had pCR. Table 2 compares the characteristics of the two groups of patients undergoing neoadjuvant chemotherapy. There was no significant difference between the two groups with regards to age, race, histology, nuclear grade, clinical T or N stage, or overall clinical stage.

Compared with patients who underwent neoadjuvant chemotherapy and had residual disease, univariate analysis showed significantly improved OS in patients receiving adjuvant therapy [HR = 0.46, 95% confidence interval (CI) 0.29–0.72, $P = 0.001$] or those receiving neoadjuvant chemotherapy with pCR (HR = 0.12, 95% CI 0.02–0.88, $P = 0.04$). OS was 77.8% for patients who received adjuvant chemotherapy, 92.3% for patients who received neoadjuvant chemotherapy with pCR, and 67.2% for patients who received neoadjuvant chemotherapy and had residual disease. Figure 1 illustrates the survival curves for the three

treatment groups. Other factors which were also associated with overall survival include clinical T and N stage and overall clinical stage. After controlling for these covariates associated with survival on univariate tests, multivariate analysis demonstrated that OS for patients receiving adjuvant therapy was prolonged compared with patients who received neoadjuvant chemotherapy and had residual disease following treatment (HR = 0.51, 95% CI 0.32–0.83, $P = 0.007$), but was not significantly different compared with those receiving neoadjuvant therapy with pCR (HR = 0.19, 95% CI 0.03–1.38, $P = 0.10$).

## DISCUSSION

In TNBC, a subtype of breast cancer with no targeted therapies, chemotherapy is the primary systemic treatment. Despite its aggressive nature, TNBC is particularly chemosensitive, with high pCR rates in the neoadjuvant setting compared with the other breast cancer subtypes. Of note, neoadjuvant chemotherapy, once used only for locally advanced breast cancer, has become more common for all types and stages of breast cancers.[15,16] It not only allows patients to undergo breast-conserving surgery who may not have otherwise, but also provides for a crucial observation of response to treatment. Despite these benefits of preoperative therapy, it is still unclear if use of neoadjuvant chemotherapy translates to improved overall survival compared with adjuvant chemotherapy in patients with TNBC.

No previous neoadjuvant chemotherapy trial has demonstrated a survival benefit or harm compared with adjuvant chemotherapy. The primary aim of NSABP protocol B-18 was to determine whether preoperative chemotherapy would result in improved OS and DFS compared with postoperative adjuvant chemotherapy. At both 9 and 16 years of follow-up there was no difference in OS and DFS between the two groups.[6,8,13,16,17] This large prospective, randomized trial did not differentiate among breast cancer subtypes, and these results have therefore been applied for all patients with breast cancer. In the most recent report of this trial, Rastogi et al.[16] make several references to the probable difference in chemotherapy response between ER+ and ER− tumors, however due to limitations of the study, hormone receptor status was not available. While several studies have investigated TNBC in isolation in the neoadjuvant chemotherapy setting, no study has directly compared neoadjuvant and adjuvant chemotherapy for this breast cancer subtype.[6,8,13,17]

Although a retrospective analysis, our study suggests an overall survival benefit in patients with pCR following neoadjuvant chemotherapy compared with patients receiving adjuvant therapy. This is despite the fact that patients receiving neoadjuvant treatment were more likely to have worse disease. As demonstrated in our prior analysis of this patient population, patients undergoing neoadjuvant chemotherapy had increased tumor size, nodal positivity, and advanced clinical stage compared with patients receiving adjuvant chemotherapy.

In our previous analysis of this population, we showed a survival advantage in patients receiving adjuvant chemotherapy compared with all patients receiving neoadjuvant chemotherapy. When interpreted with our current results and previous literature, it is suggested that the poor survival in patients receiving neoadjuvant therapy was determined by the worse survival of patients with residual cancer. In this study, we show a clear benefit of neoadjuvant chemotherapy in those patients with pCR but again confirm our previous findings that there is a subset of patients with better survival with adjuvant chemotherapy compared with neoadjuvant chemotherapy. In our retrospective analysis, we used multivariate analysis to control for factors known to affect survival and which probably also increased a patient's likelihood of receiving neoadjuvant chemotherapy. However, our

results still suggest that, by identifying patients likely not to achieve pCR, we could identify patients who may best be treated with adjuvant therapy.

Our study has several limitations. Notably, this is a retrospective study and therefore patients were not randomly selected to receive neoadjuvant or adjuvant chemotherapy. As we noted previously, younger patients with more aggressive or advanced cancers were more likely to receive neoadjuvant treatment. Further, the retrospective nature of this analysis is limited by the inability to directly compare chemosensitive tumors with chemoresistant tumors in patients receiving adjuvant chemotherapy. Perhaps patients were selected to undergo neoadjuvant chemotherapy rather than adjuvant chemotherapy because their tumors were fundamentally different (e.g., larger, higher mitotic index, etc.). We attempted to control for this in our multivariate analysis, although there still may be variables affecting survival that were not included in our multivariate analysis. The inherent heterogeneity of the tumors in the adjuvant chemotherapy group remains a significant limitation. Even with this limitation, it is noteworthy that patients who received neoadjuvant chemotherapy with pCR fared best, suggesting other factors affecting survival. Another weakness of our study is the lack of consistency of the chemotherapy regimens. The most common regimens were adriamycin and/or taxane based but varied between the three groups. Regardless, this is a fair reflection of the chemotherapy practices to date in the setting of TNBC. In a prospective analysis, a more consistent chemotherapy regimen would need to be designated during trial design.

Our data add to the growing literature about neoadjuvant chemotherapy and TNBC. It is clear that a prospective study needs to be carried out to better elucidate the indications for neoadjuvant or adjuvant chemotherapy in patients with TNBC. In our study we were unable to show any differences between the two groups of patients who underwent neoadjuvant chemotherapy which might predict their response to the therapy, but this is another interesting area of research in TNBC. Li et al.[18] recently published data indicating that certain biological markers could be helpful in predicting pCR. In 41 patients with locally advanced TNBC undergoing neoadjuvant docetaxel plus epirubicin, it was found that negative basal-like status, negative epidermal growth factor receptor status, high Ki-67 proliferation index, and positive nm23-H1 status were significantly predictive of pCR.[18] Such biologic indices may prove useful in delineating chemosensitivity during future prospective trials.

Another area of interest in chemotherapy in the setting of TNBC is the recent introduction of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors. These inhibitors block PARP, an enzyme which is involved in base-excision repair after DNA damage. Recent studies have shown encouraging activity in early trials of tumors arising in *BRCA* mutation carriers and in sporadic TNBC.[19,20] With the role of PARP inhibitors still in its infancy, results of neoadjuvant and adjuvant administration are pending.

In conjunction with other research in the neoadjuvant setting, we have shown a benefit to TNBC patients who achieve pCR. In addition, our data, and others, indicate that patients with residual disease at time of surgery have much worse outcome. Prognostically, this is important. The role of neoadjuvant chemotherapy has evolved over the past 10 years. It not only allows for improved cosmetic outcomes, but also enables medical and surgical oncologists to better assess a tumor's clinical activity. Our data corroborate a survival benefit of neoadjuvant chemotherapy in the setting of TNBC for selected patients. However, for those patients with TNBC who receive neoadjuvant therapy and do not experience pCR, the outcome is particularly poor. Future investigation of new and promising therapies for TNBC is vital so that patients with residual disease following treatment can be offered further targeted adjuvant therapy. In addition, we believe that our retrospective data provide justification for the development of a well-designed, prospective, randomized controlled

trial to demonstrate the benefits of neoadjuvant versus adjuvant chemotherapy in patients with TNBC. Based on our results, we would hypothesize that early systemic treatment prior to surgical resection improves survival for patients demonstrating chemosensitivity, and those patients who do not respond initially may benefit from expedited surgical intervention and alternative adjuvant systemic therapies.

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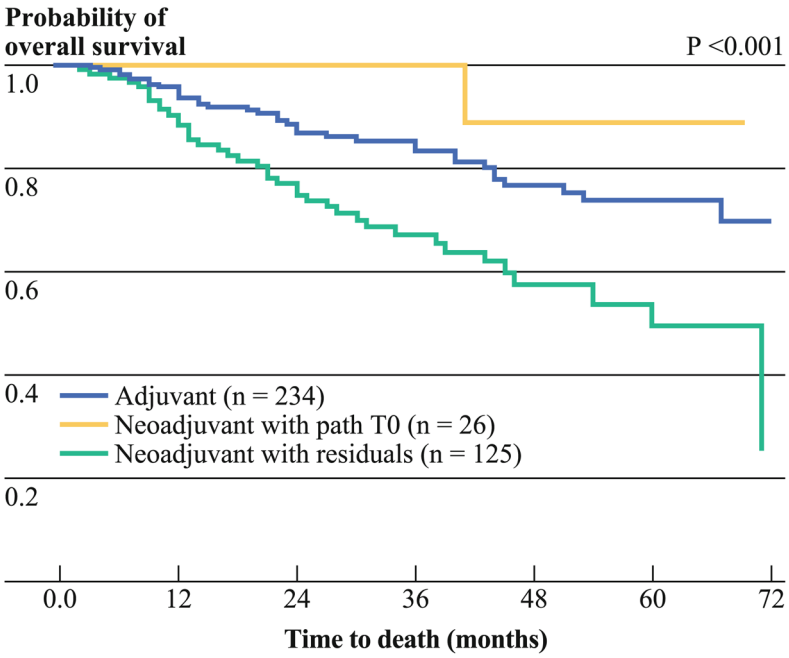


**FIG. 1.**

Overall survival comparing 385 patients according to receipt of adjuvant chemotherapy (*n* = 234), neoadjuvant chemotherapy with complete pathologic response (*n* = 26), or neoadjuvant chemotherapy with residual disease following treatment (*n* = 125)

## TABLE 1

Patient and tumor characteristics of 385 patients with triple-negative breast cancer treated between 2000 and 2008

| Characteristic | *n* (%) |
|---|---|
| Age (years) | |
| < 50 | 178 (46) |
| ≥50 | 207 (54) |
| Race | |
| Caucasian | 238 (62) |
| African–American | 138 (36) |
| Other | 9 (2) |
| Clinical T stage | |
| T1 | 122 (32) |
| T2 | 157 (41) |
| T3 | 33 (9) |
| T4 | 29 (7) |
| Other | 44 (11) |
| Histology | |
| Invasive ductal | 310 (80) |
| Invasive lobular | 14 (3) |
| Mixed/others | 61 (16) |
| Nuclear grade | |
| Grade 1 | 4 (1) |
| Grade 2 | 40 (10) |
| Grade 3 | 330 (85) |
| Unknown | 11 (3) |
| Clinical N status | |
| N0 | 226 (59) |
| N1 | 93 (24) |
| N2 | 12 (3) |
| N3 | 15 (4) |
| Unknown | 39 (10) |
| Clinical stage | |
| 1 | 91 (24) |
| 2A | 122 (32) |
| 2B | 54 (13) |
| 3 | 60 (16) |
| Unknown | 58 (15) |

## TABLE 2

Association of patient and tumor characteristics following neoadjuvant chemotherapy and pathologic complete response (pCR) versus no pCR

| Characteristic | pCR, *n* = 26 | No pCR, *n* = 125 | *P*-Value |
|---|---|---|---|
| Age (years) | | | |
| < 50 | 11 (42) | 71 (57) | NS |
| ≥50 | 15 (58) | 54 (43) | |
| Race | | | |
| Caucasian | 14 (54) | 75 (60) | NS |
| African–American | 11 (42) | 46 (37) | |
| Other | 1 (4) | 4 (3) | |
| Clinical T stage | | | |
| T1 | 5 (19) | 17 (14) | NS |
| T2 | 17 (65) | 58 (46) | |
| T3 | 2 (8) | 22 (17) | |
| T4 | 2 (8) | 20 (16) | |
| Unknown | 0 | 8 (6) | |
| Histology | | | |
| Invasive ductal | 22 (85) | 98 (78) | NS |
| Invasive lobular | 1 (4) | 6 (5) | |
| Mixed/others | 3 (11) | 21 (17) | |
| Nuclear grade | | | |
| Grade 1 | 0 (0) | 2 (2) | NS |
| Grade 2 | 1 (4) | 14 (11) | |
| Grade 3 | 24 (92) | 106 (85) | |
| Unknown | 1 (4) | 3 (2) | |
| Clinical N status | | | |
| N0 | 13 (50) | 50 (40) | NS |
| N1 | 9 (35) | 56 (45) | |
| N2 | 0 (0) | 9 (7) | |
| N3 | 5 (15) | 6 (5) | |
| Unknown | 0 (0) | 4 (3) | |
| Clinical stage | | | |
| 1 | 4 (15) | 6 (5) | NS |
| 2A | 11 (42) | 40 (32) | |
| 2B | 6 (23) | 28 (22) | |
| 3 | 5 (19) | 44 (35) | |
| Unknown | 0 | 7 (6) | |