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Neoadjuvant *Versus* Adjuvant Chemotherapy for Triple Negative Breast Cancer

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Background. **The study aim was to investigate factors that predict the use of neoadjuvant *versus* adjuvant chemotherapy in patients with triple negative breast cancer (TNBC) and the overall survival in each group.**

Methods. **We identified 493 patients with Stage I-III TNBC between 1998 and 2008. Patients were divided according to receipt of neoadjuvant, adjuvant, or none/unknown chemotherapy. Data were compared using χ^2 and Fisher's exact test. For more than two group comparisons and analyzing multiple dependent variables, MANOVA was used. Kaplan-Meier curves were generated.**

Results. **Of 493 patients with TNBC, 154 (31%) received neoadjuvant chemotherapy, 251 (51%) received adjuvant chemotherapy, and 88 (18%) had no or unknown chemotherapy. Patients undergoing neoadjuvant chemotherapy were younger (mean 50, range 20–83) compared with those undergoing adjuvant chemotherapy (mean 53, range 25–83) or none/unknown chemotherapy (mean 62, range 29–86) ($P < 0.0001$). The three groups did not differ significantly by patient race, tumor histology, or tumor grade. Increased tumor size, nodal positivity, and advanced stage were more likely to be associated with use of neoadjuvant chemotherapy (all comparisons $P < 0.0001$). After controlling for covariates associated with survival in unadjusted tests, patients undergoing adjuvant therapy were less likely to die compared with patients undergoing neoadjuvant therapy or none/unknown therapy (overall aHR 0.476, 95% CI 0.295–0.770).**

Conclusions. **Women with TNBC who underwent adjuvant chemotherapy were 52% less likely to die overall compared with those who received neoadjuvant chemotherapy or none/unknown chemotherapy in this institutional series. Prospective studies are necessary to determine if this finding is durable.**

Key Words: **breast cancer; triple negative; neoadjuvant chemotherapy; adjuvant chemotherapy.**

INTRODUCTION

Breast cancer is the most common cancer in women and is the second most common cause of cancer-related deaths in women. Breast cancer is a heterogeneous disease, and expression of steroid hormone receptors, such as estrogen receptor (ER) and progesterone receptor (PR), and the oncogene ErbB-2/human epidermal growth factor receptor 2 (HER-2), are important factors in distinguishing breast cancer subtypes. Of these subtypes, triple-negative breast cancer (TNBC), which is characterized by a lack of ER, PR, and HER-2 expression, makes up 11%–20% of all cases of breast cancer [1, 2]. TNBC is often thought of as being synonymous with basal-like breast cancer, one of the subtypes of breast cancer defined by gene expression array analysis [3]. Although studies have demonstrated that these two groups share many pathologic and clinical features, not all basal-like tumors are triple negative and not all TNBCs express basal-like gene clusters by microarray analysis [4].

TNBC is characterized by a particularly aggressive clinical course. Studies demonstrate that the triple negative or basal-like phenotype portends a worse prognosis than other subtypes of breast cancer [1, 5–11]. In randomized trials, patients with TNBC or basal-like breast cancer treated with anthracyclines and taxanes experience a significantly decreased survival compared

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with patients with other tumor types [12–14]. The aggressiveness of this disease is further established by the fact that the risk of recurrence peaks within the first 3 y and the majority of deaths take place within the first 5 y after initial treatment [15, 16]. Additionally, a significantly shorter survival is observed after diagnosis of metastatic disease in both TNBC and basal-like breast cancer [16–18]. Although the relationship between TNBC and a poorer prognosis has been supported by previous studies, the effect on risk of local and distant recurrence is less clear. However, several studies have demonstrated an increased rate of visceral *versus* bone metastasis and an increased risk of central nervous system metastases among patients with TNBC compared with non-TNBC [19–23].

In addition to the aggressive clinical history of TNBCs, options for treating this subtype of breast cancer are limited as these tumors lack a therapeutic target that can be treated with hormone therapy or trastuzumab. Therefore, chemotherapy is the standard method used to treat these patients. Previous neoadjuvant chemotherapy trials have shown that triple negative tumors are more chemosensitive than other subtypes of breast cancer, as evidenced by higher pathologic complete response (pCR) rates [11, 23]. In a large study performed by Liedtke *et al.* [19], the association between TNBC and response to several regimens of neoadjuvant chemotherapy as well as overall survival was examined in 1118 patients with early-stage breast cancer. As shown in previous studies, an increased pCR rate was seen for TNBC, but this subgroup still exhibited decreased survival rates compared with non-TNBC. However, those patients who did experience a pCR following neoadjuvant chemotherapy had significantly better overall survival than those with residual disease regardless of receptor expression. Of those with residual disease, the patients with TNBC had a decreased overall survival compared with non-TNBC patients.

Previous neoadjuvant chemotherapy trials have failed to demonstrate a significant survival advantage over the use of adjuvant chemotherapy. However, these studies include patients of all receptor status. The aim of the current study was to investigate the factors which predict the use of neoadjuvant chemotherapy *versus* adjuvant chemotherapy in patients with TNBC and to determine whether any survival benefit is observed with either approach.

METHODS

Study Design

Institutional review board approval was obtained prior to the commencement of this retrospective study. Written informed consent of patients was not required. The prospectively maintained surgical database at Washington University/Barnes Jewish Hospital was queried from January 1, 2000 to June 31, 2008 to identify all patients with a diagnosis of stage I-III [according to American Joint Committee on Cancer guidelines [24] biopsy-proven invasive TNBC ($n = 493$). Patients were divided according to receipt of neoadjuvant chemotherapy, adjuvant chemotherapy, or none/unknown chemotherapy for the analysis.

Pathologic Assessment

Pathologic diagnosis, ER status, PR status, and HER-2/neu status were determined by core biopsy prior to systemic therapy or surgical therapy. ER and PR 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.

Statistical Analyses

Categorical data were compared using Fisher's exact and chi squared tests. P values < 0.05 were considered statistically significant. Univariate analysis was used to estimate the effects of clinical and pathologic characteristics on receipt of neoadjuvant *versus* adjuvant *versus* none/unknown chemotherapy. To identify variables independently associated with the use of neoadjuvant *versus* adjuvant *versus* none/unknown chemotherapy use, a multivariate analysis using MANOVA was performed. All variables with a P value < 0.20 in the univariate analysis were included in a logistic regression model, allowing for interaction. Overall survival (actual), defined from the date of diagnosis to the date of death from any cause, was estimated with the Kaplan-Meier method. All analyses were performed with SAS ver. 9 (SAS Institute, Cary, NC).

RESULTS

During the study period from 2000–2008, 493 patients with TNBC were treated at our institution and included in the analysis. Patient and tumor characteristics are shown in Table 1. Of 493 patients with TNBC, 154 (31%) received neoadjuvant chemotherapy, 251 (51%) received adjuvant chemotherapy, and 88 (18%) received no chemotherapy or had unknown chemotherapy.

Table 2 is a summary of the relationship between clinicopathologic factors and the receipt of neoadjuvant chemotherapy *versus* adjuvant chemotherapy *versus* none/unknown chemotherapy. Patients undergoing neoadjuvant therapy were younger (mean 50 y, range 20–83) compared with those undergoing adjuvant therapy (mean 53 y, range 25–83) or no chemotherapy (mean 62 y, range 29–86) ($P < 0.0001$). There was no difference between the groups according to race. The three groups did not differ significantly by tumor histology or tumor grade. Increased tumor size (T2, T3, T4), nodal positivity, and advanced stage (IIB, III) were more likely to be associated with use of neoadjuvant chemotherapy (all comparisons $P < 0.0001$). There were no significant differences between the types of

TABLE 1

Patient and Tumor Characteristics of 493 Patients with Triple Negative Breast Cancer Treated Between 2000 and 2008

Characteristic	*n* (%)
Age	
<50	230 (47%)
≥50	263 (53%)
Race	
Caucasian	300 (61%)
African-American	184 (37%)
Other	9 (2%)
Clinical T stage	
T1	149 (30%)
T2	195 (40%)
T3	64 (13%)
T4	25 (5%)
Unknown	60 (12%)
Histology	
Invasive ductal	393 (80%)
Invasive lobular	51 (10%)
Mixed/others	49 (10%)
Nuclear grade	
Grade 1	7 (1%)
Grade 2	59 (12%)
Grade 3	406 (83%)
Unknown	21 (4%)
Clinical N status	
N0	198 (40%)
N1	232 (47%)
N2	14 (3%)
N3	5 (1%)
Unknown	44 (9%)
Clinical stage	
1	149 (30%)
2A	142 (29%)
2B	57 (12%)
3A	32 (6%)
3B	15 (3%)
3C	19 (4%)
Unknown	79 (16%)
Type of surgical therapy	
Lumpectomy	272 (55%)
Mastectomy	221 (45%)

chemotherapy administered in the neoadjuvant and adjuvant treatment groups. The most common regimens in both groups were adriamycin and/or taxane-based regimens. Patients who received no or unknown systemic therapy were more likely to have clinical and pathologic T1, N0, and stage I pathology.

Mean follow-up for the study population was 4.3 ± 1.7 y; the follow-up period did not differ significantly between the three treatment groups. After controlling for all covariates associated with survival in unadjusted tests, patients undergoing adjuvant therapy were less likely to die during the follow-up period compared with patients undergoing neoadjuvant therapy or none/unknown therapy (overall aHR 0.476, 95% CI 0.295–0.770). After excluding the patients who received no or unknown systemic therapy, the overall survival difference persisted, whereby patients undergoing adjuvant therapy were less likely to die compared with patients undergoing neoadjuvant therapy (overall aHR 0.480, 95% CI 0.298–0.774). Figure 1 illustrates the survival curves between the three treatment groups (the survival curves with no/unknown therapy excluded are similar for the neoadjuvant and adjuvant groups and are not shown).

DISCUSSION

TNBC is an aggressive subtype of breast cancer that lacks a therapeutic target, making chemotherapy the primary systemic modality used in the treatment of this disease. The use of neoadjuvant chemotherapy for this sub-group of patients has risen in recent years, likely as a result of recent studies demonstrating that TNBC is more chemosensitive than other subtypes of breast cancer [25–28]. Further, the response of the tumor to neoadjuvant chemotherapy provides important prognostic information, whereby patients with a pCR in both the breast and axillary lymph nodes fare better than those with residual disease [19, 25, 26]. However, it is unclear which patients with TNBC are more likely to experience a pCR and whether the use of neoadjuvant chemotherapy translates to improved overall survival compared with adjuvant chemotherapy.

The current study illustrates several patient and tumor characteristics, which are more likely to result in the use of neoadjuvant chemotherapy compared with adjuvant chemotherapy in the setting of TNBC. We identified four independent factors associated with receipt of neoadjuvant chemotherapy: young age, increased tumor size, nodal positivity, and advanced stage. These findings are not surprising and corroborate previous reports. It has been suggested that younger women receive greater benefits from treatment with neoadjuvant therapy than older women [28]. The NSABP Protocol B-18 demonstrated a trend in favor of preoperative chemotherapy for DFS and OS in women less than 50 y old (HR = 0.85, $P = 0.09$ for DFS; HR = 0.81, $P = 0.06$ for OS). Neoadjuvant chemotherapy is also increasingly used at our institution and others for locally-advanced breast cancer to reduce the primary tumor size, and potentially permit breast-conserving therapy [27]. However, we were surprised to find that those patients with TNBC who received adjuvant chemotherapy had improved overall survival compared with those who received neoadjuvant chemotherapy, after controlling for age, tumor size, nodal status, and stage. There are several possible hypotheses to explain these findings.

No previous neoadjuvant chemotherapy trial has ever demonstrated a survival benefit or detriment

TABLE 2

Association of Patient and Tumor Characteristics with Use of Neoadjuvant *versus* Adjuvant *versus* None/ Unknown Chemotherapy

Characteristic	Neoadjuvant $n = 154$	Adjuvant $n = 251$	None/unknown $n = 88$	P value
Age				
<50	96 (62%)	105 (42%)	29 (33%)	<0.0001
≥50	58 (38%)	146 (58%)	59 (67%)	
Race				
Caucasian	94 (61%)	155 (62%)	51 (58%)	NS
African-American	53 (34%)	95 (38%)	36 (41%)	
Other	7 (5%)	1 (0%)	1 (1%)	
Clinical T stage				
T1	3 (2%)	89 (35%)	57 (65%)	
T2	80 (52%)	101 (40%)	14 (16%)	<0.0001
T3	43 (28%)	19 (8%)	2 (2%)	
T4	20 (13%)	5 (2%)	0 (0%)	
Unknown	8 (5%)	37 (15%)	15 (17%)	
Histology				
Invasive ductal	130 (84%)	198 (79%)	65 (74%)	NS
Invasive lobular	14 (10%)	28 (11%)	9 (10%)	
Mixed/others	10 (6%)	25 (10%)	14 (16%)	
Nuclear grade				
Grade 1	0 (0%)	5 (2%)	2 (2%)	
Grade 2	14 (9%)	34 (14%)	11 (13%)	NS
Grade 3	135 (88%)	197 (78%)	74 (84%)	
Unknown	5 (3%)	15 (6%)	1 (1%)	
Clinical N status				
N0	30 (19%)	126 (50%)	72 (82%)	
N1	91 (59%)	105 (42%)	14 (16%)	<0.0001
N2	19 (13%)	9 (4%)	0 (0%)	
N3	12 (8%)	2 (1%)	0 (0%)	
Unknown	2 (1%)	9 (3%)	2 (2%)	
Clinical stage				
1	3 (2%)	105 (42%)	41 (47%)	
2A	53 (34%)	75 (30%)	14 (16%)	
2B	37 (24%)	16 (6%)	4 (5%)	<0.0001
3A	22 (14%)	9 (4%)	1 (1%)	
3B	15 (10%)	0 (0%)	0 (0%)	
3C	15 (10%)	4 (2%)	0 (0%)	
Unknown	9 (6%)	42 (16%)	28 (31%)	
Type of surgical therapy				
Lumpectomy	79 (51%)	119 (47%)	74 (84%)	NS
Mastectomy	75 (49%)	132 (53%)	14 (16%)	

compared with adjuvant chemotherapy. The National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-18 set out to determine differences in overall survival and disease-free survival between neoadjuvant and adjuvant treatment of all subtypes of breast cancer [27, 28]. This study demonstrated that through 9 and 16 y of follow-up, the outcome for patients treated with preoperative chemotherapy is similar to the outcome for those treated with standard adjuvant chemotherapy. However, previous neoadjuvant trials represent a heterogenous group of patients with multiple tumor subtypes. The results of the current study may be unique to the TNBC subtype, whereby inclusion of this subgroup of patients with other non-TNBC tumor groups may mask the survival differences observed in previous analyses.

It is clear from previous studies that TNBCs display higher rates of pCR following neoadjuvant chemotherapy, a major determinant of clinical outcome, than non-TNBC [11, 25–28]. However, in the setting of residual disease after neoadjuvant treatment, the overall prognosis of this disease is still poor. Carey *et al.* [11] found that TNBC and HER2+ breast cancers displayed much higher rates of pCR (27% and 36%, respectively), compared with the luminal subtype, which had a pCR rate of 7% ($P = 0.01$). Additionally, Liedtke *et al.* [19] performed a large study of 1118 patients with early-stage breast cancer and found that patients with TNBC had significantly higher pCR rates (22% *versus* 11%; $P = 0.034$), but decreased 3-year progression-free survival rates ($P < 0.0001$) and 3-year overall survival rates ($P < 0.0001$) compared

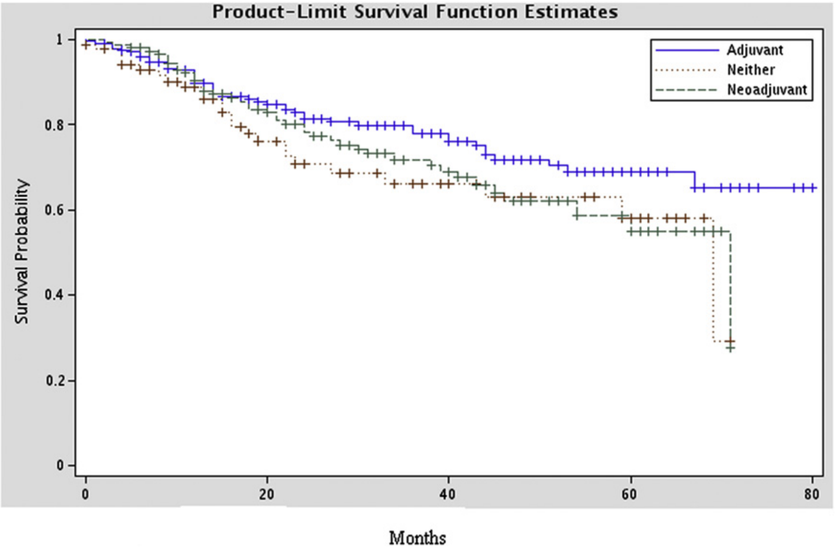

FIG. 1. Overall survival comparing 493 patients according to receipt of neoadjuvant chemotherapy ($n = 154$), adjuvant chemotherapy ($n = 251$), or none/unknown chemotherapy ($n = 88$).

with non-TNBC. If pCR was achieved, patients had similar overall survival regardless of receptor expression. However, patients with residual disease had worse overall survival if they had TNBC compared with non-TNBC ($P < 0.0001$). Therefore, although TNBC has been shown to be more chemosensitive, there is no evidence to support that this chemosensitivity translates to improved survival in the neoadjuvant setting compared with the adjuvant setting.

Because there is no survival benefit for patients with TNBC who undergo neoadjuvant chemotherapy, the current study findings may be explained by a "delay effect" in those receiving neoadjuvant chemotherapy. In other words, leaving the primary tumor and/or axillary metastases intact during neoadjuvant chemotherapy may result in systemic tumor seeding. TNBCs may also demonstrate a higher metastatic potential, with an increased propensity for visceral *versus* bone metastasis and an increased risk of central nervous system metastases compared with non-TNBCs [19–23]. The observed survival benefit of adjuvant chemotherapy may be a result of earlier tumor debulking and decreased opportunity for systemic tumor shedding and growth of systemic micrometastases. Colleoni *et al.* [29] demonstrated an improved survival for premenopausal patients with ER negative tumors who had early initiation of adjuvant chemotherapy (within 20 d after surgical therapy) *versus* those who had delayed initiation of adjuvant chemotherapy (21–86 d after surgical therapy). The same benefit was not observed for premenopausal patients with ER positive tumors. Therefore, the benefit of primary tumor removal followed by early initiation of adjuvant therapy may be most relevant for the TNBC subgroup.

This study has a number of limitations. We are unable to provide disease-free survival data due to inherent limitations of the database and are restricted to overall survival analyses. It is a retrospective analysis, and it is difficult to interpret the complex decision-making surrounding the selection of patients for neoadjuvant *versus* adjuvant treatment. The patient sample is heterogeneous with regard to stage, histology, and chemotherapy protocols utilized. The patients underwent many variable neoadjuvant or adjuvant chemotherapy regimens based on individual patient and tumor characteristics. Further, the types of regimens and delivery methods may have changed during the relatively long study period. We are unable to control for these variations in the current retrospective analysis. There is also potential for selection bias as those patients with smaller tumors, node-negative disease, or early-stage cancers were more often offered adjuvant chemotherapy. The impact of selection bias is difficult to assess retrospectively. Although we attempted to control for such variables in our multivariable model, it is possible that other factors not included in the model may have contributed to certain patients being selected for the neoadjuvant *versus* adjuvant groups. These limitations may explain the observed difference in overall survival between patients treated with neoadjuvant *versus* adjuvant chemotherapy.

Despite these limitations and after controlling for these variables in multivariable analyses, the current study demonstrates that women with TNBC who underwent adjuvant chemotherapy were 52% less likely to die overall compared with those who received neoadjuvant chemotherapy or none/unknown chemotherapy. A prospective, randomized trial is imperative in order to determine the best approach for this unique breast cancer subtype.

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