Ann Surg Oncol (2016) 23:1537–1542
DOI 10.1245/s10434-015-5039-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

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ORIGINAL ARTICLE – BREAST ONCOLOGY

Factors Affecting the Completion of Adjuvant Chemotherapy in Early-Stage Breast Cancer

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ABSTRACT

Background. Despite the survival benefit associated with adjuvant chemotherapy in early-stage breast cancer, many do not complete treatment. This study identified factors associated with noncompletion of adjuvant chemotherapy among a select population of women with early-stage breast cancer.

Methods. The study sample was obtained from a multicenter study designed to evaluate patient-assistance program usage among early-stage breast cancer patients requiring adjuvant therapy. In this study, 333 patients with stages I and II breast cancer undergoing surgery from October 2006 to September 2009 completed 6-month follow-up surveys assessing their experiences with care, health status, social support, self-efficacy, and treatment beliefs. In- and outpatient medical records were abstracted to assess treatment completion. Of the 333 patients, 198 initiated adjuvant chemotherapy and formed our study cohort. The study compared patients who did and did not complete adjuvant chemotherapy.

Results. The median patient age was 53 years (range 28–86 years). According to self-identification, 41 % of the patients were non-Hispanic white and 21 % were black. A total of 13 patients (7 %) did not complete adjuvant chemotherapy. In the bivariate analysis, the patients not completing chemotherapy were more likely to be black and unmarried women with low emotional social support and a poor body image after treatment. In the multivariate analysis, black race [odds ratio (OR) 5.62; 95 % confidence interval (CI) 1.63–20.36] and poor body image (OR 9.75; 95 % CI 2.12–95.95) were independently associated with noncompletion of chemotherapy.

Conclusions. Overall chemotherapy noncompletion rates were low among women exposed to patient-assistance programs. However, poor body image and black race were independent predictors of uncompleted chemotherapy. The true impact of race in this group may result from social factors that occur more often among black women, including poor social support.

Despite declining incidence rates during the last decade, breast cancer remains the most common cancer diagnosed among women in the United States, with an estimated 231,840 cases of invasive breast cancer[1] and 40,200 breast cancer deaths expected in 2015. The use of adjuvant chemotherapy for early-stage breast cancer has improved both breast cancer-specific survival and overall survival,[2–4] yet many women do not complete their recommended chemotherapy regimens. Failure to complete chemotherapy is documented to range from 3 % in a study showing self-reported compliance[5] to 36 % in a report using the Surveillance, Epidemiology, and End Results (SEER) database of patients with early-stage breast cancer treated between 1992 and 2005.[6] Given the large number of women affected by the disease and up to one third of women failing to complete adjuvant treatment, efforts to

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Presented in part as a poster presentation at the 68th Society of Surgical Oncology Annual Cancer Symposium, 25–28 March 2015, Houston, TX.

Electronic supplementary material The online version of this article (doi:10.1245/s10434-015-5039-5) contains supplementary material, which is available to authorized users.

First Received: 21 September 2015;

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identify factors associated with noncompliance and to improve rates of chemotherapy completion are needed.

Prior studies seeking to identify patient groups at high risk for failure to complete chemotherapy have yielded conflicting results, with some studies identifying black race as a risk factor[7,8] and others identifying it as a protective factor.[9] Other variables such as older age, insurance type, marital status, medical comorbidities, and mistrust of the medical system also have been reported as risk factors for failure to complete chemotherapy.[9–11] However, these factors may be influenced by patient resources and access to care.

In an effort to identify risk factors not influenced by patient resources and access to care, this study examined factors associated with noncompletion of chemotherapy among a selected population of women enrolled in a multicenter study designed to assess the impact of patient assistance programs on disparities in care.[12]

METHODS

Patients with newly diagnosed stages I and II breast cancer who underwent breast surgery between October 2006 and September 2009 and initiated adjuvant chemotherapy were identified from a previously published multi-institutional randomized controlled trial population. Institutional review board approval was obtained.[12]

The parent randomized trial, conducted among eight inner-city hospitals, was designed to test the effectiveness of patient assistance programs in reducing disparities in care. Patients participating in the parent study were asked to complete a baseline needs assessment survey (2–4 weeks after surgery) and a follow-up survey 6 months later evaluating their experiences with care, health status, social support, self-efficacy, and treatment beliefs.

Of 658 women eligible for the parent study, 374 (57 %) completed the baseline survey, and records were abstracted for all of them. Of these patients, 333 (89 %) completed the 6-month survey. Overall, 198 (59 %) of these women initiated adjuvant chemotherapy, thus forming our study cohort (Fig. 1). Patients with a history of breast cancer and those receiving neoadjuvant therapy were excluded from the study. Chart abstractors tracked care using previously described methods[13] and abstracted in- and outpatient charts for adjuvant treatment received within 1 year after surgery.

The number of chemotherapy cycles planned was compared with the number of cycles completed at the time of chart abstraction to determine rates of chemotherapy completion.

Chi square, *t* tests, Wilcoxon Rank test, and Fisher's exact tests were used for bivariate comparisons between patients who completed adjuvant chemotherapy and those who did not. The factors evaluated included demographics (age, race, level of education, insurance, marital status), clinical characteristics (surgery type, tumor size, receptor status, comorbidities, side effects), physical and emotional factors (instrumental and emotional social support, mental and physical health), and perceptions/treatment beliefs (body image, self-efficacy, fatalism, beliefs about chemotherapy) from the 6-month survey.

The presence of comorbidities was defined as a Charlson Comorbidity Index of 1 or higher.[14] Side effects included change in weight, cognitive functioning, difficulty sleeping, difficulty breathing, fatigue, hair loss, numbness or tingling, dry skin, and other. Instrumental social support (ISS), emotional social support (ESS), self-efficacy, and fatalism were assessed by conceptual validated scaled questions.[15,16] The specific survey questions related to side effects, ISS, ESS, perceptions, and treatment beliefs can be found in Supplementary Table 1. The 12-Item Short Form Health Survey (SF-12), a standardized health assessment tool, was used to measure mental and physical health.[17] Poor body image was defined as a new onset of unhappiness with body appearance after treatment.

A multivariate model to identify independent predictors of noncompletion of chemotherapy was generated using clinical factors significant in the univariate analysis or previously reported to have an impact on treatment completion. All p values lower than 0.05 were considered significant.

RESULTS

Among the 333 women completing both the baseline and 6-month follow-up survey in the parent study, 201 initiated adjuvant chemotherapy treatment, and complete data regarding planned and completed cycles of chemotherapy were available for 198 patients. The median patient age was 53 years (range 28–86 years). According to self-identification, 20.7 % of the patients were black, and 41.4 % were non-Hispanic white. The majority of the patient cohort had commercial health insurance (61 %) and education levels above high school (80.8 %). The median tumor size was 1.8 cm (range 0.3–6.7 cm), and 50 patients (25 %) had triple-negative breast cancer. Surgical treatment included mastectomy for 109 patients (55 %), 68 (62.3 %) of whom also had reconstruction (6 delayed, 62 immediate).

The largest group of patients received Adriamycin-cyclophosphamide-Taxotere (47 %), followed by TC (20 %), AC (14 %), and CMF (7 %). Noncompletion of all planned chemotherapy was documented for 13 patients (7 %), 10 (77 %) of whom completed at least 75 % of their planned

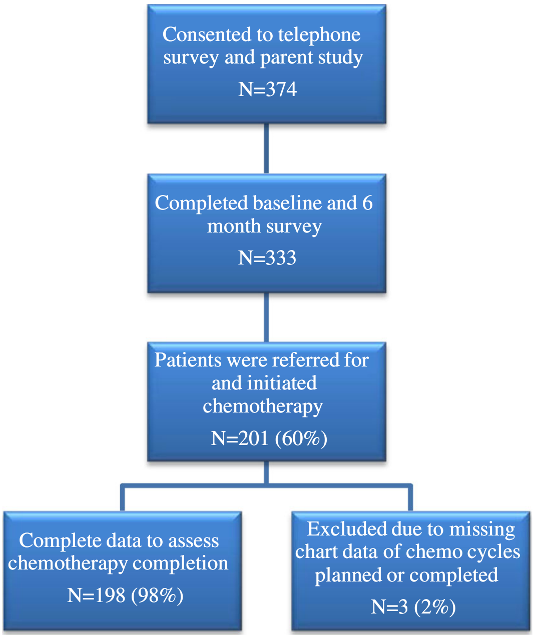

FIG. 1 CONSORT flowchart

cycles before discontinuing treatment. Chart review found that 3 of 13 patients cited neuropathy as the reason for stopping treatment. Five patients cited other side effects. Four patients discontinued treatment due to comorbidities, and one patient had no reason for stopping treatment. The patient survey found that 5 of the 13 women who did not complete chemotherapy reported being too sick ("nearly died") or having side effects ("problems with bones" and "bad rash") as reasons for noncompletion. The remaining eight women did not report a reason for not completing chemotherapy.

Factors Associated with Noncompletion of Chemotherapy

Compared with those who completed chemotherapy, the patients who did not complete chemotherapy were more likely to be black ($p = 0.01$) and unmarried ($p = 0.04$) (Table 2). Tumor size, receptor status, type of surgery, employment status, level of income, presence of comorbidities, and treatment-related side effects were not associated with noncompletion of chemotherapy.

In the bivariate analysis, low levels of emotional social support were associated with noncompletion of chemotherapy, yet the same relationship was not true for instrumental social support (Table 1) (Supplementary Table 1). The survey questions assessing postchemotherapy perceptions and beliefs found only poor body image after treatment to be significantly associated with noncompletion of treatment ($p = 0.01$).

In the multivariate analysis, poor body image after treatment [odds ratio (OR) 9.75; 95 % confidence interval (CI) 2.12–95.95] and black race (OR 5.62; 95 % CI 1.63–20.36) were independently associated with noncompletion of chemotherapy (Table 2).

DISCUSSION

Low rates for noncompletion of chemotherapy were found among women with a new early-stage breast cancer. The few women who did not complete the full course of chemotherapy were more likely to perceive a poor body image and to be black.

Previous studies examining rates for noncompletion of chemotherapy have yielded a wide range of results, likely reflecting differences in methodology and access to resources in the populations studied. Ruddy et al.[5] reported the lowest rate for noncompletion of chemotherapy (3 %) based on patient-reported dosing calendars, which are maintained by patients themselves and inherently subject to social desirability and recall bias. They defined rates of nonadherence as the number of patient-reported doses of oral cyclophosphamide taken over the number prescribed. Lipscomb et al.[9] reported a 10 % rate of incomplete chemotherapy based on electronic data abstraction and case-by-case author review focusing on the question "Did the chemotherapy received match the plan?"

In contrast, the highest nonadherence rate (36 %) was reported from the SEER database,[6] in which complete adjuvant chemotherapy was defined as 6 months of treatment, was not cycle dependent, and included data from a period longer than 20 years (1992–2005). This report demonstrates that among a selected population of women with early-stage breast cancer participating in a randomized trial designed to assess the impact of patient assistance programs, the rate for noncompletion of chemotherapy was relatively low (7 %). Yet identifiable predictors of noncompletion of treatment still exist, even among women who all have received uniform information about their cancer, its treatment, and available resource assistance programs.

The majority of patients in our cohort who did not complete chemotherapy were unmarried (77 %), initially indicating a significant effect of marriage on chemotherapy completion ($p = 0.04$). However, in the multivariate analysis, marriage was no longer significant and did not contribute to the final model. This raised the question whether it was the emotional aspects of marriage or the practical aspects of marriage that influenced the ability to complete chemotherapy. On further investigation, we found that unmarried women were more likely to be black ($p = 0.002$), to have Medicaid insurance ($p = 0.001$), and

TABLE 1 Univariate analysis of demographics, clinical factors, and side effects

	Did not complete CT ($n = 13$) n (%)	Completed CT ($n = 185$) n (%)	p Value
Median age: years (range)	53.0 (41–86)	53.0 (28–82)	0.35
Black	7 (53.9)	34 (18.4)	0.01[a]
Education less than high school	5 (38.5)	33 (17.8)	0.14
Medicaid	6 (46.2)	42 (22.7)	0.09[b]
Income < $30,000[c]	7 (63.6)	61 (37.4)	0.11
Unemployed[c]	6 (46.2)	59 (32.6)	0.37
Married	3 (23.1)	104 (56.2)	0.04
Median tumor size: cm (range)	2.1 (0.8–3.2)	1.7 (0.3–6.7)	0.64
ER/PR positive	8 (61.5)	129 (69.7)	0.54
HER2 positive	0 (0)	28 (15.1)	0.32
TNBC	5 (38.5)	45 (26.0)	0.34
Mastectomy	4 (30.8)	105 (56.8)	0.09
Comorbidities (score $\geq$ 1)	4 (30.8)	21 (11.4)	0.06
Side effects			
Change in weight	10 (76.9)	114 (62.3)	0.38
Cognitive change	8 (61.5)	94 (51.7)	0.57
Difficulty sleeping	11 (84.6)	126 (68.9)	0.35
Difficulty breathing	5 (38.5)	56 (30.4)	0.55
Fatigue	9 (69.2)	136 (73.9)	0.75
Hair loss	11 (84.6)	173 (94.0)	0.21
Numbness or tingling	9 (69.2)	139 (75.5)	0.74
Dry skin	8 (61.5)	123 (66.9)	0.76
Other symptoms	6 (46.2)	83 (45.9)	1.00
Health status			
SF-12 mental score: n (range)	49.3 (26.5–70.8)	49.9 (12.9–71.8)	0.83
SF-12 physical score: n (range)	40.4 (16.0–56.3)	45.8 (7.1–67.2)	0.10
Perceptions & beliefs			
Instrumental social support[d]	71.5 (20–100)	74.3 (20–100)	0.70
Emotional social support[d]	72.3 (46.7–100)	83.6 (26.7–100)	0.04
Fatalism[d]	78.5 (20–100)	82.2 (20–100)	0.62
Self-efficacy[d]	81.2 (30–100)	82.4 (25–100)	0.79
Poor body image	12 (92.3)	99 (53.8)	0.01

CT chemotherapy, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *TNBC* triple-negative breast cancer, *SF-12* 12-Item Short Form Health Survey

[a] Comparison is made between black and non-black

[b] Comparison is made between any Medicaid and all other insurance. Although 11 patients did not provide insurance information and 5 patients were identified as uninsured, none of these patients failed to complete chemotherapy

[c] A total of 174 patients reported their income (24 had missing data) and 181 reported their employment status (4 had missing data)

[d] Mean scores with their respective ranges in parenthesis

to have lower instrumental support ($p = 0.004$) as well as lower emotional support ($p = 0.03$), highlighting the complex relationships that exist for many women facing a breast cancer diagnosis and its treatment.

Our study and others continue to highlight the importance of racial disparities in breast cancer treatment and outcomes[18,19] yet this is not solely limited to women who identify as black. Rates of incomplete chemotherapy among different racial groups as reported to the SEER database were comparable: 38 % among non-Hispanic blacks, 36 % among non-Hispanic whites, 36 % among Hispanics, and 40 % among Asian/Pacific Islanders.[6] We found that a significantly larger proportion of black versus non-black women (17 vs. 4 %; $p < 0.04$) did not complete

TABLE 2 Multivariate analysis of factors affecting completion of adjuvant chemotherapy[a]

Factor	OR	CI	*p* Value
Black	5.62	1.63–20.36	0.01
Medicaid	3.53	0.87–14.90	0.07
Poor body image	9.75	2.12–95.94	0.01
Comorbidities	4.29	0.82–21.36	0.07
Emotional social support	0.99	0.96–1.02	0.34

OR odds ratio, *CI* confidence interval

[a] Model $c = 0.872$ ($p < 0.0001$)

chemotherapy. However, black women who had high levels of emotional social support were more likely to complete treatment than those who did not. Thus, even among a group of women who were provided information about cancer treatment and assistance programs, an individual's social connection was an important factor in her ability to complete treatment.

Others also have shown that treatment delays due to missed appointments,[7] health insurance status, symptom severity, and depressive symptoms are associated with the decision to adhere to chemotherapy among black women and Caucasian women alike.[11] In contrast, a study focused on women in rural southwest Georgia showed that black race was positively associated with completion of care. Black patients received or completed chemotherapy at rates equal to or exceeding those for Caucasian patients.[9] Thus, although race may be a risk factor for noncompletion, it likely serves as a proxy for other critical yet remediable risk factors.

Although some postulate that women may not complete chemotherapy treatment due to financial limitations,[20–23] we did not find finances to affect adherence. Patients with incomes lower than $30,000 and those unemployed or having only Medicaid were just as likely to finish treatment as their counterparts. In fact, the five uninsured women in the sample all completed treatment. It should be noted, however, that all our participants were treated in New York State, a state with generous Medicaid eligibility and coverage as well as a strong social service network.

Somewhat surprisingly, patient-reported chemotherapy side effects were not significantly associated with nonadherence in this cohort. Although others have found that a decline in health-related quality of life during therapy predicted early treatment discontinuation (even after accounting for age and side effects),[24] we did not find such associations. Interestingly, patients' beliefs about the efficacy of treatment also were not associated with noncompletion of chemotherapy, although this factor was associated with treatment initiation in an earlier publication from one of our authors.[10] These conflicting findings may have been due to the limited sample size of the current analysis or, alternatively, may suggest that perceptions interfering with the willingness to begin treatment likely differ from those that disrupt treatment completion.

A significant proportion of the women in our cohort (56 %) were unhappy with treatment-related changes in their appearance, and poor body image was significantly associated with noncompletion of chemotherapy. Type of surgery (mastectomy vs breast conservation) did not appear to influence body image even when reconstruction was taken into account. Given these findings, counseling or psychosocial programs that address the body image of patients undergoing breast cancer surgery and adjuvant chemotherapy may represent an opportunity to identify women at increased risk for not completing treatment, thus providing an opportunity to intervene.

We acknowledge that our study may have limited generalizability because of the method used to ascertain the patient population, which included women in an urban area who consented to participate in a clinical trial. Patients participating in clinical trials may not represent the general public. In fact, the treatment rates in our trial were quite high in both the usual care and intervention arms, 92 and 95 %, respectively, with no significant difference by treatment arm ($p = 0.4$). The high treatment rates in both trial arms support the notion that patients participating in clinical trials may differ from the general population.

Due to the small sample size, the study had limited power to definitively ascertain the impact of factors on chemotherapy completion. Although our population did have access to care, as all had received surgery and at least some chemotherapy, a significant portion of the women were living in poverty with limited resources. Yet, we were able to demonstrate that even in a best case scenario population of women participating in a clinical trial, all of whom received information regarding patient assistance programs, noncompletion of chemotherapy remains a problem, and continued efforts to understand the complex relationships between race, social support, and emotional support are warranted. Notably, the average time between chemotherapy completion and the patient survey was 113 days, and patient recall of symptoms may have changed during that time.

CONCLUSION

The rates for noncompletion of chemotherapy among women with newly diagnosed early-stage breast cancer were low among women exposed to patient assistance programs. Poor body image and black race were independent predictors of noncompletion of chemotherapy. However, the true impact of race in this group may have resulted from a combination of factors that occur more often among black women, including poor social support.

ACKNOWLEDGMENT This study was funded by Mount Sinai's Center for Health Equity and Community Engaged Research and the Cary Grossman Breast Research Fellowship.

DISCLOSURE There are no conflicts of interest.

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