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Enrollment onto breast cancer therapeutic clinical trials: A tertiary cancer center experience

Suzanne Swain-Cabriaes, MSN^a, Laura Bourdeanu, PhD^b, Joyce Niland, PhD^c, Tracy Stiller, PhD^c, and George Somlo, MD^{d,*}

^aClinical Research Office-Medical Oncology, Cedars Sinai-Samuel Oschin Cancer Center, Los Angeles, CA, USA

^bDepartment of Nursing, The Sage Colleges, Troy, NY, USA

^cDivision of Biostatistics, Department of Information Sciences, COHCC, Duarte, CA, USA

^dDepartment of Medical Oncology and Experimental Therapeutics, City of Hope Cancer Center (COHCC), Duarte 91010–3000, CA, USA

Abstract

Background—Advances in breast cancer prevention, diagnosis, and treatment are in part the result of patient involvement in clinical trials. Despite increases in new clinical research initiatives and trials open to accrual, only 2–3% of women with breast cancer enroll. There is a need to identify the barriers interfering patient accrual.

Methods—Data were extracted from patients with breast cancer seen for treatment in 2009 retrospectively. Descriptive analysis of patient demographic on enrollment were performed using logistic regression analyses.

Results—Of 418 patients evaluated for treatment, 163 had a trial available; 138 of these were eligible. Eighty (58%) participated in a clinical trial; the remainder declined (24%) or were not presented for a trial by their treating physicians (76%). Age, preferred language, marital status, family history, or race/ethnicity did not predict for enrollment on a therapeutic clinical trial. Patients with stage II or III breast cancer were more likely to be enrolled on a trial compared to patients with stage 0 or I (odds ratio 2.89, 9.17; $p=.02$, .0005 respectively).

Conclusions—Enrollment of breast cancer patients on therapeutic clinical trials was relatively high (58% eligible, 19% overall). Prospective studies observing breast cancer stage, clinical trial design, and inclusion of community based physician practices would add breadth to the understanding of poor accrual to breast cancer clinical trials.

Keywords

Breast cancer; Clinical trials; Cancer prevention; Clinical trial accrual; Trial barriers; Accrual

The American Cancer Society estimated that 229,060 new cases of invasive cancer would be diagnosed in 2012 (Siegel, Naishadham, & Jemal, 2012). With only lung cancer exceeding the number of breast cancer deaths in women, it was estimated that 39,920 women would die from breast cancer in that year (Siegel et al., 2012). Advances in breast cancer prevention, diagnosis and treatment are the direct result of patient involvement in

therapeutic and non-therapeutic clinical trials. The success of these trials depends on enrolling the statistically required number of subjects and keeping them on study until the trial has been completed (Mills et al., 2006). Despite increases in the numbers of new clinical research initiatives and trials open to accrual, only 2–3% of women with breast cancer ever enroll in a clinical trial and an even smaller fraction enroll onto adjuvant therapy studies (Melisko et al., 2005). Poor recruitment to clinical trials leads to delays in study completion and slows down the approval of more effective cancer treatments for patients with all stages of cancer (Wright et al., 2004).

Several studies have identified the potential barriers that may impact clinical trial enrollment among cancer patients. Both patient- and healthcare provider-barriers have been found to hinder the enrollment in clinical trials. Mistrust of the health care system is the most often cited patient-barrier encountered in clinical research, followed by patient bias against clinical trials, poor performance status, comorbidities, insurance, and transportation issues (Ford et al., 2005). Several clinician-oriented factors pertinent to participation rates have been identified, including clinician's awareness and access to available clinical trials, clinician's bias to a particular treatment modality, clinician's concern of losing patients to follow-up, and lack of compensation (Mansour, 1994). Ethnic minority and older women are less likely to be offered clinical trials or be eligible for clinical trials. Patients with recurrences or who received prior or current treatment are more likely to be considered ineligible for clinical trials. Another factor associated with a higher likelihood of enrollment in clinical trials is the stage of the cancer, with stage IV showing higher enrollment than stages I, II, or III (Simon et al., 2004). Availability of appropriate clinical trials, delays in opening trials and restrictive eligibility criteria are additional barriers to enrollment in clinical trials (Mansour, 1994).

Several interventions have been developed to minimize these barriers and increase accrual in clinical trials. However, no new studies have assessed whether these interventions have been effective in increasing accrual into clinical trials. This study was therefore undertaken to identify the clinical trial accrual pattern among all newly diagnosed adult breast cancer patients at a tertiary cancer center located in the greater Los Angeles area over a 1-year period. In addition, some potential barriers to clinical trial enrollment were identified.

1. Materials and methods

A retrospective chart review was utilized for this study. Data were extracted from the medical records of patients with all stages of breast cancer who were consecutively seen at City of Hope Medical Center (COH) for treatment in 2009. Permission to conduct the study was obtained from the Institutional Review Board (IRB) at COH in accordance with the Health Insurance Portability and Accountability Act (HIPAA). The retrospective analysis consisted of data collected from 418 patients with histologically confirmed breast cancer seen at COH in 2009. Data collected included age, stage of breast cancer, preferred language, ethnicity, marital status, and family history of breast cancer. Appropriate studies at the time of initial consultation were obtained from the COH database based on the histologic subtype and staging. A formal individualized eligibility review was then conducted. Patients who presented for a second opinion regarding treatment and did not go on to receive therapeutic treatment at COH were excluded from the analysis. Along with descriptive analysis of patient demographic data, logistic regression was also performed to determine odds ratio estimates using a univariate model of all patient variables. Statistical software used included R (v. 2.12.1) and Statistical Package for the Social Sciences, version 17.0 (SPSS, Inc., Chicago, IL).

2. Results

Of the 418 patients seen in consultation by the medical oncologists at COH in 2009, only 163 had a trial available to them, with 138 being eligible for the available trial. Lack of trial availability limited enrollment for 39% of the patients who presented with breast cancer. Eighty of the 138 eligible patients, (58%) participated in clinical trials. The remainder (58, 42%) either declined trial participation despite meeting eligibility criteria (14/58, 24%), or were not considered for clinical trials by their treating physicians (44/58, 76%).

The overall median age was 54 years (range: 29–92). Patient's preferred languages were grouped as either English ($n=113$) or other ($n=25$). Other languages consisted of Arabic, Armenian, Chinese-Taiwanese, Korean, Russian, and Spanish. Of the 138 patients who were eligible for a trial, the majority were White-non Hispanic (49%), with the remainder being were Hispanic (29%), Black (8%), and Asian (14%). Breast cancer was assessed as stages 0–I, II, III, and IV with most patients being diagnosed with early stage (0–I, II, and III) breast cancer (72%). By marital status, the majority of the patients were married (57%) with the remainder being single, divorced, widowed, or separated. Most of the patients did not have a family history of breast cancer (56%), while a third of the patients had only one family member with cancer. The remainder of the patients had two or more family members with cancer or were unaware of their family history.

By univariate analysis (Table 1), no difference was found between patients enrolled and patients not enrolled on a trial based on age, preferred language, marital status, family history, or race/ethnicity. Stage of breast cancer was the only factor significantly associated with being enrolled on a trial. Patients with stage II breast cancer were 2.9 times as likely to be enrolled on a trial compared to patients with stage 0 or I (95% confidence interval [CI] 1.2–7.1, $p=0.02$). Patients with stage III breast cancer were 9.2 times as likely to be enrolled on a trial compared to patients with stage 0 or I (95% CI 2.7–31.8, $p=.0005$). There was no difference in the likelihood of being enrolled on a trial for patients with stage IV breast cancer compared to patients with stage 0 or I ($p=.15$).

3. Discussion

This study investigated the clinical trial accrual pattern among all newly diagnosed adult breast cancer patients. While enrollment of eligible breast cancer patients onto therapeutic clinical trials at City of Hope Medical Center is high (80/138, 58%), overall the proportion of breast cancer patients eligible for clinical trials remains low (80/418, 19%), predominantly due to lack of availability of a suitable trial. Lack of trial availability was a rate-limiting factor in enrollment on breast cancer clinical trials in 61% of our patients. This is similar to the findings by Simon et al. (2004) of 41 to 67% (Simon et al., 2004). The 19% accrual rate is higher than the reported 2–3%, demonstrating that the cancer clinical trial accrual rate has not remained stagnant, despite the lack of availability of a suitable trial.

Barriers to enrollment on clinical trials were previously reported as lack of physician time, lack of dedicated research staff, restrictive eligibility criteria, and lack of insurance coverage for patients participating in clinical trials (Schilsky, 2011). The stage of the cancer was also found to affect participation on clinical trials. Patients with earlier stage disease were less likely to participate in a trial in part due to a sense of loss of control. Conversely, those with advanced disease with presumably fewer treatment options were more likely to consider treatment on a clinical trial (Simon et al., 2004). The data collected at City of Hope Medical Center closely mirrored the aforementioned data in that early stage breast cancer patients are less likely to enroll to cancer trials. This discrepancy in enrollment between early stages and late stages could be due to fact that the current outcomes of stage I breast cancer with

standard of care therapy have driven the focus of breast cancer research to be on later stages of the disease.

Other studies have suggested that lower socio-economic status, ethnic minorities, patients with language barriers, and/or racial minorities are hesitant to participate in clinical trials because of doubt regarding the efficacy of the experimental agent (Millon-Underwood, Sanders, & Davis, 1993; Murthy, Krumholz, & Gross, 2004). Historical experiences with clinical trials and levels of education are also potential barriers to participation in clinical trials (Murthy et al., 2004). Our study found no difference between patients enrolled and patients not enrolled on a trial with respect to preferred language, or race/ethnicity. Education level was not evaluated in this study.

Clinical trials are an important step in translating potentially beneficial laboratory research findings into clinical practice. Attempts, such as awareness campaigns, clinical trial registries and Web based search engines, and accruals of adults onto cancer clinical trials have been made to improve patient accruals onto clinical trials. This study revealed that these attempts have been successful, with enrollment in clinical trials being markedly higher than other reports. Although improved, the rate of enrollment remains low (19%). Barriers to cancer clinical trial accrual should be prospectively identified and addressed in future studies, with the hope of leading to more vigorous enrollment. Additionally, prospective studies observing breast cancer stage, clinical trial design, and inclusion of community based physician practices would add breadth to the understanding of poor accrual to breast cancer clinical trials. Understanding of these barriers will, in turn, allow the development of interventions to increase enrollment in clinical trials and potentially improve outcomes in cancer patients.

There are several limitations that could potentially affect the validity of this study. The data were not collected prospectively in a standardized fashion, thus the charting may potentially have been missing data regarding the reason for failure of a patient to enroll in a clinical trial and the percentages reported may be a misrepresentation of the true values. In addition, the patients in this study were chosen consecutively and thus there may have been an unequal distribution of patient-related variables. Finally, the patient population included only patients treated at one Southern California institution in 2009, and thus had the population distribution at that specific place and time. It is likely that patient populations evaluated at a different point in time or elsewhere would possess different characteristics.

3.1. Clinical implications

The recruitment of breast cancer participants for research studies is often a challenge. Nurses are frequently persons whom patients trust most in the healthcare experience and, therefore have the ability to be successful in this endeavor. Nurses must be prepared to discuss thoroughly any concerns of prospective trial participants.

The results of this study demonstrate a significant increase in clinical trial enrollment, hence nurses must be aware, informed, and able to perform the functions related to clinical trials. Nurses should be prepared to identify patients eligible for clinical trials and be fully aware of the specific aspects of a particular trial in order to discuss in detail with potential participants. By knowing the basics of clinical trials, nurses may be able to improve participation rates in clinical trials and advocate for clinical research.

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Table 1

Effect of demographic and disease characteristics on clinical trial enrollment.

	Enrolled on a clinical trial (n=80) n (%)	Not enrolled on a clinical trial (n=58) n (%)	Odds ratio (95% CI)	p-Value ^a
Age				
<50	31 (38.7)	20 (34.5)		
50	49 (61.3)	38 (65.5)	0.83 (0.41–1.68)	.61
Stage of breast cancer				
Stage 0–I	15 (18.8)	25 (43.1)		
Stage II	26 (32.5)	15 (25.9)	2.89 (1.17–7.12)	.02
Stage III	22 (27.5)	4 (6.9)	9.17 (2.65–31.76)	.0005
Stage IV	17 (21.2)	14 (24.1)	2.02 (0.78–5.25)	.15
Preferred language				
English	66 (82.5)	47 (81.0)		
Other	14 (17.5)	11 (19.0)	0.91 (0.38–2.17)	.83
Marital status				
Married	44 (55.0)	35 (61.4)		
Single	15 (18.8)	11 (19.3)	1.09 (0.44–2.66)	.86
Separated/ divorced/ widowed	21 (26.2)	11 (19.3)	1.52 (0.65–3.57)	.34
Unknown	0	1		
Family history				
None	45 (57.7)	33 (58.9)		
1 family member	24 (30.8)	21 (37.5)	0.84 (0.40–1.75)	.63
2+ family members	9 (11.5)	2 (3.6)	3.30 (0.67–16.29)	.14
Unknown	2	2		
Race/ethnicity				
White-non Hispanic	37 (46.3)	30 (51.7)		
Hispanic	25 (31.2)	15 (25.9)	1.35 (0.61–3.01)	.46
Black	6 (7.5)	5 (8.6)	0.97 (0.27–3.50)	.97
Asian	12 (15.0)	8 (13.8)	1.22 (0.44–3.36)	.71

^a p-Value by logistic regression analysis.