Adherence and Persistence With Oral Adjuvant Chemotherapy in Older Women With Early-Stage Breast Cancer in CALGB 49907: Adherence Companion Study 60104

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ABSTRACT

Purpose

Patient adherence is critical in evaluating the effectiveness of an oral therapy. We sought to measure adherence among women randomly assigned to capecitabine in a preplanned substudy of a multicenter clinical trial.

Patients and Methods

Cancer and Leukemia Group B study CALGB 49907 was a randomly assigned trial comparing standard chemotherapy versus oral chemotherapy with capecitabine in patients age 65 years or older with early-stage breast cancer. We used microelectronic monitoring system (MEMS) caps on participants' capecitabine bottles to record pill bottle openings. Capecitabine was given in two divided daily doses for 14 consecutive days of a 21-day cycle for six cycles. Adherence was calculated as the number of doses taken divided by doses expected, taking into account toxicity-related dosing changes. A participant was defined as adherent if 80% or more of expected doses were recorded by MEMS.

Results

Overall, 161 patients were enrolled. Median age was 71 years (range, 65 to 89 years); 124 patients (83%) persisted with capecitabine to completion of planned protocol therapy. Adherence was 78% across all cycles, and adherence did not vary by cycle ($P = .32$). Twenty-five percent of participants took fewer than 80% of expected doses and were nonadherent. In a logistic regression model, participants with node-negative disease ($P = .01$) and mastectomy ($P = .01$) were more likely to be nonadherent. Adherence was not related to age, tumor stage, or hormone receptor status. Adherence was not significantly associated with relapse-free survival or grade 3 or 4 toxicity.

Conclusion

Most older women with early-stage breast cancer were adherent to short-term oral chemotherapy in a randomized clinical trial. Age was not associated with adherence.

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INTRODUCTION

Patient nonadherence to oral antineoplastic therapy is a well-recognized barrier to effective treatment. Yet, inability to adhere to oral antineoplastic agents has only recently received increased attention on the part of the oncology community.^{1,2} Little is known about adherence with oral chemotherapy, as it is rarely rigorously assessed in trials. Clinical trials evaluating oral cancer therapy traditionally rely on self-report or pill diaries as the primary measure of adherence. Self-reported adherence, however, has been shown to overestimate adherence.^{3,4} The use of

microelectronic monitoring system (MEMS) caps, a relatively new innovation that records date and time that the cap of a pill bottle is removed as a surrogate for taking a dose of the medication inside, has revealed that patient self-report, as well as pill count, generally overestimate adherence.^{3,5-7} Valid assessment of patient adherence, the extent to which a patient acts in accordance with the prescribed interval and dose of a regimen, is critical in evaluating the effectiveness of an oral therapy.⁸ In cancer, as with other diseases, there may be substantial variability in adherence to prescribed oral drug regimens, including taking fewer or more doses than prescribed or

variation in timing of doses from day-to-day.⁶ In the care of an individual patient, nonadherence may lead to a physician wrongly determining that a drug has been ineffective or to a toxicity that may have been avoidable. In the setting of a clinical trial, nonadherence has potential serious public health implications, as it may lead to inaccurate conclusions about the effectiveness or toxicity of a drug regimen.

The Cancer and Leukemia Group B (CALGB) designed a randomized trial specifically for women with early-stage breast cancer age 65 years and older to compare the efficacy between standard chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) or doxorubicin and cyclophosphamide (AC) with the oral fluorouracil prodrug capecitabine.⁹ Patients with stages I to IIIB breast cancer were randomly assigned to standard chemotherapy or capecitabine, and the primary trial end point was relapse-free survival.

To additionally explore quality of life and adherence in this unique population, a subset of women were enrolled onto a preplanned quality-of-life (QOL) companion study (CALGB 70103). All women enrolled on the QOL study who were randomly assigned to capecitabine were offered participation in this preplanned adherence companion study (CALGB 60104).

The primary objectives of the adherence study were to measure adherence to capecitabine and to examine relationships between aging and adherence. It was hypothesized that, as age increases, there would be a significant decrease in adherence to the prescribed oral dosing regimen, given that previous research suggests that adherence to oral anti-breast cancer therapy is associated with patient age.¹⁰⁻¹²

PATIENTS AND METHODS

Women participating in CALGB 49907 who were randomly assigned to capecitabine and consented to the QOL companion study were then asked to participate in the adherence study (Fig 1). Each participant signed an institutional review board–approved, protocol-specific informed consent in accordance with federal and institutional guidelines. MEMS caps on participants' capecitabine bottles were used to record each time a patient opened the bottle to take capecitabine, and the patients were instructed to open their pill containers only when taking a dose. (Fig 2: graphic of MEMS cap and reader

Fig 2. Microelectronic monitoring system (MEMS) cap and pill bottle with computer cap reader.

system) Adherence was calculated as the number of doses taken as measured by MEMS divided by the number of doses planned per protocol taken, considering toxicity-related dosing changes as documented by study staff. Unless capecitabine was stopped for toxicity, 28 doses of capecitabine were planned for each of the six planned cycles.

Definitions

On the basis of prior medication adherence research, a participant was defined as nonpersistent if she came off therapy without completing the protocol-specified treatment and was defined as nonadherent if fewer than 80% of doses expected were recorded by MEMS for capecitabine. A missed dose of capecitabine was defined as no redosing within 20 hours from the previous dose, when another dose was planned as per protocol. A dosing violation was defined as a dose taken less than 8 hours or more than 16 hours, but less than 20 hours, from the previous dose. In a more conservative consideration of dosing violations, a 10- to 14-hour window was explored.

Statistical Methods

The overall objectives of the study were to measure adherence to capecitabine and to explore the relationship between age and adherence to capecitabine. Adherence was averaged for all participants, with complete capecitabine data for all cycles available for each cycle. Trends over time with cycle number were conducted by using analysis of variance (ANOVA) for repeated measures. To explore the relationship between age and adherence to capecitabine, univariate linear regression analysis was used, as well as a multivariate logistic regression model to evaluate predictors of 80% or greater adherence. Poisson regression was used in a test for trend in the number of violations by age. The Kaplan-Meier product limit was used to estimate relapse-free survival, and the relationship between adherence and incidence of grade 3 or 4 toxicity was explored by using the Fisher exact test. The accrual goal was 184 for the study of adherence to capecitabine. Patient registration, random assignment, and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson. Statistical analyses were performed by CALGB statisticians with SAS software, version 9.1 (SAS Institute, Cary, NC).

Fig 1. CONSORT flow diagram of participants. QOL, quality of life; CALGB, Cancer and Leukemia Group B; MEMS, microelectronic monitoring system.

RESULTS

CALGB 49907 opened for accrual on September 15, 2001, and it was closed to accrual in November 2006, when a preplanned boundary for futility was crossed. The clinical trial was stopped after the first planned analysis of 600 patients showed that capecitabine therapy was highly likely to be inferior to standard chemotherapy with longer follow-up (hazard ratio, 0.53; probability of a hazard less than 0.80 with continued accrual of 90%). Patients randomly assigned to capecitabine were two times more likely to experience relapse ($P = .0006$) and were almost two times more likely to die ($P = .019$). Thus, standard therapy was concluded to be superior to capecitabine in patients age 65 years and older who had early-stage breast cancer.

At that time, 633 patients had been accrued to the clinical trial, 307 of whom were randomly assigned to adjuvant capecitabine (Fig

1). Three hundred sixty-seven patients in the clinical trial accepted participation in the QOL substudy, and 161 of the 174 women on capecitabine in the QOL substudy consented to participate in the adherence companion study (Fig 1). Patient characteristics are listed in Table 1. In an analysis comparing all patients randomly assigned in the entire trial but not in the adherence study compared with those in the adherence study, there were no significant differences between the two groups in terms of their demographics or baseline characteristics (Table 1). Of women on the adherence study, 150 had complete data, including complete forms and MEMS cap data, for any cycles on therapy (Fig 1). Women with complete data ($n = 150$) did not differ from those with incomplete data ($n = 11$) by age, ethnicity, performance status, type of surgery, tumor stage, nodal status, or hormone receptor status.

Persistence With Protocol Therapy

Among the 150 women for whom we had data to measure adherence, 124 patients (83%) persisted with capecitabine to completion of planned protocol therapy (ie, six cycles of capecitabine). The remaining 26 patients (17%) did not complete six cycles of protocol therapy; 17 ended early because of toxicity, adverse effects, or complications; five patients withdrew from the study (three of them before receiving any treatment and two after beginning treatment); two patients had disease progression or experienced relapse during active treatment; and two were incomplete as a result of deaths on study.

Adherence With Capecitabine

Average adherence was 78% across all cycles for all patients with complete data for any cycle ($n = 150$), and average adherence was not significantly associated with cycle number ($P = .41$) in a test for trends over time (Fig 3). Figure 4 presents average adherence among participants for all six cycles, and it demonstrates that average adherence varied widely between participants, including some participants taking less than 10% of prescribed therapy compared with a large majority who took 100% of study drug.

Age as a continuous variable was not associated with adherence in a linear regression model. When patients were grouped dichotomously by average adherence, 25% of participants took

Table 1. Baseline Participant Demographic and Clinical Characteristics for Patients Randomly Assigned to Capecitabine, Broken Down by Participation in the Adherence Study

Variable	Adherence Study Participants (n = 161)		CALGB 49907 Participants Not on Adherence Study (n = 472)		P (Fisher's exact test)
	No.	%	No.	%	
Ethnicity					
White	137	85	401	85	1.00
Other	24	15	71	15	
Hispanic or Latino	3	2	27	6	.09
Non-Hispanic	138	86	399	85	
Unknown	20	12	46	10	
Age, years					
65 to 69	62	39	156	33	.39
70 to 79	88	55	286	61	
80 to 89	11	7	30	6	
ECOG performance status					
0	114	71	343	73	.18
1	40	25	121	26	
2	7	4	8	2	
Most extensive primary surgery					
Partial mastectomy/ lumpectomy/ excisional biopsy	79	49	209	45	.62
Mastectomy, NOS	82	51	263	55	
Hormone receptor status					
Negative	49	31	154	33	.70
Positive	112	69	318	67	
Tumor size, cm*					
≤ 2	63	39	220	47	.21
2-5	89	56	226	48	
> 5	9	6	26	6	
Axillary lymph node status					
Positive	111	69	326	70	.69
Negative	50	31	135	29	
Unknown			11	1	

Abbreviations: CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.
*Tumor sizes are associated with T stage as follows: T1, ≤ 2 cm; T2, 2-5 cm; and T3, > 5 cm.

Fig 3. Adherence among participants by cycle using the microelectronic monitoring system (MEMS).

Fig 4. Distribution among participants of percent adherence over six cycles using the microelectronic monitoring system (MEMS).

fewer than 80% of expected doses. In a multivariate logistic regression model of participants with 80% or greater average adherence, participants with node-positive disease were more likely to be adherent ($P = .01$), as were those who received partial mastectomy/lumpectomy/excisional biopsy ($P = .01$). Nonsignificant covariates were age, ethnicity, performance status, tumor size, and hormone receptor status, and all covariates were grouped as in Table 1 unless otherwise stated.

Dosing Violations

Among the 150 patients with complete data, there were 22,336 doses recorded by MEMS. Seven hundred thirty-six dosing violations were recorded (3.3%), and these violations occurred in 99 of the patients (66%). In the more conservative analysis of dosing violations, which used a shorter window, there were 2,373 dosing violations in 22,336 doses (ie, 10.6% were violations) occurring in 127 of the patients (85%). There were 262 missed doses (1.2%) occurring in 99 patients (66%). In a test for trend in the number of violations by age, there were no significant correlations between any of the following violations and age: number of violations (using the conservative window; $P = .13$); number of missed doses ($P = .48$); or number of violations and missed doses ($P = .10$).

Adherence and Outcomes

Average individual participant adherence, either dichotomized at 80% or greater ($P = .21$) or as a continuous variable ($P = .36$), was not associated with relapse-free survival. However, the small number of events observed within a small sample size (ie, only nine events occurred in the under 80% group) limits the interpretation of this finding. Seventeen percent of participants considered nonadherent ended treatment early because of toxicity compared with 5% of those considered adherent, and this was statistically significant ($P = .04$). Overadherence (as measured by MEMS caps recording more frequent doses than planned) was found in 11% of patients ($n = 16$) at any point in the treatment. Neither patient overadherence ($P = .84$) nor 80% or greater adherence ($P = .12$) were associated with experience of a grade 3 or 4 toxicity.

DISCUSSION

Patient nonadherence is the ultimate barrier to treatment effectiveness.^{13,14} As a greater number of oral medications are tested and made available for the treatment of patients with cancer, adherence has been recognized as an important consideration in interpreting outcomes in both individual patients as well as in the context of clinical trials.^{1,15} In women with breast cancer, several recent studies have revealed that adherence with oral adjuvant hormonal therapy can vary substantially, and this can have a potentially adverse effect on outcomes, including survival.^{12,16-21} Few studies have looked rigorously at oral chemotherapy adherence in breast cancer treatment.²²

In this large study using MEMS caps to measure real-time adherence, the finding that the majority of women were adherent to adjuvant capecitabine is consistent with previous studies of adherence with oral therapies in women with breast cancer.^{3,12,17,22} Although the majority of patients missed at least one dose across the six cycles of therapy, only a small fraction of doses were missed overall. Nonetheless, a substantial minority of patients took less than 80% of prescribed doses of therapy. This may have important implications for future studies of oral chemotherapy.

In contrast to previous research, in this study of women age 65 years and older, age was not associated with adherence.¹⁰⁻¹² In addition, predictors of adherence were few, and future work to explore more fully the factors that may be associated with adherence, including the psychosocial state of the patient, intentions to adhere, and system and treatment-related factors, is clearly warranted.

The knowledge among participants that adherence was being measured, as well as the use of the MEMS cap for measurement, may have promoted adherence among some women.^{23,24} In addition, clinical trial participants tend to be a select group of patients who have more support, and their behavior may not reflect typical behavior of individuals outside of a clinical trial.²⁵ Thus, adherence as measured in this study may overestimate adherence to oral chemotherapy in the real world, as it appears to do so with hormonal therapy in the adjuvant setting.^{12,16-20} To date, there are few data on adherence to oral breast cancer chemotherapy outside of a clinical trial. In this trial, patients had excellent performance status and organ function and were not representative of the entire population of patients with breast cancer in this age group. In addition, the majority of prior studies finding differences by age in women with breast cancer have evaluated chronic hormonal therapy, rather than short-term chemotherapy.

Although nonadherence was not associated with the primary clinical outcome, shorter relapse-free survival, the sample size was limited for this outcome, and there were a limited number of events. Thus, this finding should be considered uncertain; additional follow-up and a greater number of relapse events may help clarify this issue. The lack of association between significant toxicity and adherence is reassuring, as there have been concerns about overadherence with oral chemotherapy (ie, taking therapy more often or for a longer duration than indicated). We were unable to measure how many pills were taken at a time or if there were errors in dosing by using MEMS cap technology. In addition, opening a MEMS cap may not equal actual ingestion of a dose of drug. In addition, the fact that some participants were missing data (eg, MEMS caps or study forms missing) may have introduced bias, though such missing data was minimal and appeared to be random as a result of study staff rather than caused

by patient factors in most instances. Nevertheless, MEMS cap technology is considered to be less subjective to patient manipulation than other direct measurement of adherence and provides precise detail regarding the timing of dosing, which may be particularly important in evaluating efficacy and toxicity of antineoplastic therapy.⁴

In conclusion, accurate assessment of adherence in this large, randomized clinical trial was critical to interpretation of the primary outcome of the study—efficacy of capecitabine in comparison to standard chemotherapy. Future clinical trials evaluating oral agents for the treatment of cancer should consider including rigorous measurement of adherence to improve understanding of the benefits and risks of any oral therapy for patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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