Treatment Adherence and Its Impact on Disease-Free Survival in the Breast International Group 1-98 Trial of Tamoxifen and Letrozole, Alone and in Sequence

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Published online ahead of print at www.jco.org on May 23, 2016.

For the Breast International Group 1-98 Collaborative and International Breast Cancer Study Groups.

The Breast International Group 1-98 trial was financed by Novartis and coordinated by the International Breast Cancer Study Group. Support for the International Breast Cancer Study Group was provided by Swedish Cancer Society, The Cancer Council Australia, Australian New Zealand Breast Cancer Trials Group, Frontier Science and Technology Research Foundation, Swiss Group for Clinical Cancer Research, National Cancer Institute Grant CA-75362, Cancer Research Switzerland/Oncosuisse, and the Foundation for Clinical Cancer Research of Eastern Switzerland.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT00004205.

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0732-183X/16/3421w-2452w/\$20.00

DOI: 10.1200/JCO.2015.63.8619

ABSTRACT

Purpose

To investigate adherence to endocrine treatment and its relationship with disease-free survival (DFS) in the Breast International Group (BIG) 1-98 clinical trial.

Methods

The BIG 1-98 trial is a double-blind trial that randomly assigned 6,193 postmenopausal women with hormone receptor–positive early breast cancer in the four-arm option to 5 years of tamoxifen (Tam), letrozole (Let), or the agents in sequence (Let-Tam, Tam-Let). This analysis included 6,144 women who received at least one dose of study treatment. Conditional landmark analyses and marginal structural Cox proportional hazards models were used to evaluate the relationship between DFS and treatment adherence (persistence [duration] and compliance with dosage). Competing risks regression was used to assess demographic, disease, and treatment characteristics of the women who stopped treatment early because of adverse events.

Results

Both aspects of low adherence (early cessation of letrozole and a compliance score of < 90%) were associated with reduced DFS (multivariable model hazard ratio, 1.45; 95% CI, 1.09 to 1.93; $P = .01$; and multivariable model hazard ratio, 1.61; 95% CI, 1.08 to 2.38; $P = .02$, respectively). Sequential treatments were associated with higher rates of nonpersistence (Tam-Let, 20.8%; Let-Tam, 20.3%; Tam 16.9%; Let 17.6%). Adverse events were the reason for most trial treatment early discontinuations (82.7%). Apart from sequential treatment assignment, reduced adherence was associated with older age, smoking, node negativity, or prior thromboembolic event.

Conclusion

Both persistence and compliance are associated with DFS. Toxicity management and, for sequential treatments, patient and physician awareness, may improve adherence.

J Clin Oncol 34:2452-2459. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Breast cancer is the most common female malignancy worldwide, with 1.7 million diagnoses and half a million deaths annually.^{1,2} However, survival has improved successively in the last 50 years, in part because of effective adjuvant treatments. For hormone-sensitive breast cancer, clinical trials have repeatedly shown that oral hormonal treatment taken once per day for 5 years reduces recurrence risk and increases survival,³ with recent demonstration of further gains with 10 years of treatment.^{4,5} The Breast International Group (BIG) 1-98

trial demonstrated that letrozole for 5 years has an overall survival advantage compared with tamoxifen for 5 years^{6,7}; sequenced treatment (tamoxifen followed by letrozole or vice versa) is adequate for intermediate-risk patients; and the four schedules (5 years of tamoxifen, letrozole, or a sequence) are equivalent for low-risk patients.⁸

Limited investigation of the influence of treatment adherence on these improved outcomes has been undertaken. Although several randomized studies^{4,5,9} and the Oxford Overview^{10,11} demonstrate the superiority of longer-duration adjuvant endocrine treatment, suggesting that early

discontinuation would reduce benefit, only a few retrospective studies demonstrate an association between compliance and cancer-related outcomes.¹²⁻¹⁶ Nevertheless, these studies suggest breast cancer outcomes are potentially compromised by poor adherence. However, the level of adherence required to avoid a reduced benefit is unknown, and comparison of adherence to tamoxifen versus an aromatase inhibitor (AI) or sequenced treatment is also limited.^{3,12} The relationship between compliance and persistence on outcomes in endocrine clinical trials has not been investigated. We have undertaken an analysis of treatment adherence in the BIG 1-98 study to investigate its effect on disease-free survival (DFS), the influence of type of endocrine treatment on adherence, and reasons for reduced adherence.

In the study of treatment adherence, terminology definitions vary, and investigation is hampered by the accuracy of the methods used to assess adherence.¹⁷⁻¹⁹ In this article, we use adherence as an overarching term to encompass two components: taking the medication for the recommended duration (persistence) and as prescribed with respect to dose and regularity (compliance), as defined by Dezii.²⁰ In the BIG 1-98 trial, full compliance consists of taking a dose of either letrozole 2.5 mg or tamoxifen 20 mg once per day, and full persistence consists of a duration of 54 to 60 months. Compliance and persistence data were prospectively collected on case report forms.

METHODS

BIG 1-98, a phase 3, double-blind, clinical trial,²¹ randomly assigned 8,010 postmenopausal women with hormone receptor–positive early breast cancer. The four-arm option opened to accrual in April 1999 and closed in May 2003. In this option, 6,193 women were randomly assigned to receive one of four treatments: tamoxifen or letrozole for 5 years, tamoxifen (2 years) followed by letrozole (3 years), or letrozole (2 years) followed by tamoxifen (3 years). This analysis is based on 6,144 women in the four-arm

option who received at least one dose of treatment (Fig 1). All participants provided written informed consent. Ethics committees and relevant health authorities approved the protocol.

Adherence to Endocrine Therapy

Persistence is defined as the duration of protocol treatment on the basis of the dates that protocol treatment started and stopped. The prescribed treatment duration was 60 months; however, any patient who completed at least 54 months of therapy was classified as having completed treatment, which is the operational definition for this report.

Compliance is defined as the consistency of taking protocol treatment. Treatment drug packs were distributed every 6 months. A patient was compliant for a drug pack if she took at least 80% of the pills during each 6-month interval, with no breaks of 7 days or more for any reason.⁷ Pill count data were recorded for each drug pack, although this information was collected retrospectively before early 2003, reducing the reliability of compliance data in early patients.

Statistical Methods

End points. DFS is defined as the time from the date patients are randomly assigned to the date of the first proven invasive recurrence at any site, new invasive contralateral breast cancer, second nonbreast malignancy, or death from any cause.

DFS and persistence.

Analyses of early treatment cessation. In this analysis, a patient was considered to have stopped therapy early if treatment cessation was not due to treatment completion or with a DFS event. Follow-up for each patient was divided into intervals corresponding to study visits, which occurred approximately every 6 months during the trial and yearly thereafter. If a patient stopped treatment during a 6-month interval for reasons unrelated to treatment completion or a DFS event, she was reclassified as off treatment during that time interval and in all subsequent time intervals. Patients who were randomly assigned to tamoxifen monotherapy were excluded from this analysis because of the complexity added by the option of selective crossover in that treatment arm.

Marginal structural Cox regression models. The investigation of early treatment cessation is complicated by the fact that patients who

Fig 1. CONSORT diagram showing the derivation of the 6,144 women in the analytic cohort. Let, letrozole; Tam, tamoxifen.

stopped treatment early may define a group with different disease characteristics or risk factors compared with patients who completed treatment; therefore, it can no longer be assumed that the resulting two groups are comparable. In addition, a condition or event that led to early treatment cessation may also influence DFS. To address the possible interrelationships in the data between treatment cessation, the individual's disease characteristics and risk factors, and outcome, marginal structural Cox proportional hazards models (MSM) were used.²²

This modeling technique requires two steps. The first step creates time-varying weights for each patient over time, taking into account her unique medical, demographic, and treatment history. Estimation of the time-varying weights is based on multivariable logistic regression models to predict who would cease treatment during a given time interval. The numerator of each weight is modeled using baseline demographic, disease, and treatment factors. The denominator of each weight is modeled using the baseline factors in addition to time-varying risk factors such as high-grade adverse events (AEs) that occurred during protocol therapy.

In the second step, associations between early treatment cessation and DFS were estimated using Cox models with time-varying weights. The weighted Cox models were stratified by chemotherapy use. The simple version of the model had an indicator for early treatment cessation and treatment as predictors; the multivariable model included early treatment cessation, breast cancer disease characteristics, and treatment. Associations are reported as hazard ratios (HRs) with accompanying 95% Wald CIs.

Unadjusted survival using estimates of Anderson-Simon-Makuch are presented, given the unsuitability of Kaplan-Meier estimates for the time-varying effect of early treatment cessation.^{23,24} We chose a clinically relevant landmark of 3 years.

Compliance. To quantify compliance, a global score was created for each patient, defined as the percentage of drug packs where at least 80% of pills were taken with no breaks longer than 1 week. The complete analytic sample was divided into two groups: those with a compliance score $\geq 90\%$ versus $< 90\%$ of dispensed packs taken per protocol. The division at 90% was chosen retrospectively on the basis of an algorithmic approach proposed by Contal and O'Quigley using the log-rank statistic.²⁵ The algorithm was applied to 250 bootstrap samples and the median (90%; range, 75% to 100%) used as the division point in the analysis.

The relationship between compliance and DFS was explored using a conditional landmark analysis and Cox proportional hazards model on the landmark sample with compliance score as the predictor. The subsequent DFS of women who completed treatment and were disease free was compared according to compliance score.

Analysis of factors associated with early treatment cessation. Cumulative incidence curves in the presence of competing risks were used to describe time to cessation of treatment. Competing risks regression²⁶ was used to assess demographic, disease, and treatment characteristics of the women who stopped treatment early because of AEs. All treatment arms, including tamoxifen monotherapy, were included in this analysis. Competing events in the model were: cessation of treatment due to treatment completion, death, selective crossover, recurrence of disease, or other/unknown reasons. Factors considered as possible predictors of early treatment discontinuation included patient factors (age; body mass index; race; smoking status; type of menopause; or history of thromboembolic event, hypertension, bone fracture, cardiac or cerebrovascular disease, or diabetes), disease factors (nodal status, tumor grade, estrogen receptor and/or progesterone receptor status, peritumoral vascular invasion, tumor size, and site of primary tumor), prior therapy (radiation, chemotherapy, bisphosphonates, and type of local therapy), and logistic factors (year randomly assigned and geographic region). HRs are presented with 95% CIs. The statistical comparison of the cumulative incidence curves used Gray's test.²⁷ All analyses used SAS 9.2 (SAS Institute, Cary, NC) except for competing risks analyses, which used R Version 2.10 (The R Foundation for Statistical Computing).

RESULTS

Treatment Persistence and DFS

A total of 18.9% of patients did not complete endocrine treatment for reasons other than recurrence, death, or selective crossover (Table 1), with differences among treatments.

Letrozole monotherapy. Patients who received letrozole and stopped treatment early had a significantly increased hazard of

Table 1. Protocol Endocrine Treatment Adherence

	All (N = 6,144)	Treatment Assignment (Blinded)			
		Tam* (n = 1,541)	Let (n = 1,535)	Tam-Let (n = 1,541)	Let-Tam (n = 1,527)
Persistence, No. (%) patients					
Completed treatment	4,367 (71.1)	1,050 (68.1)	1,145 (74.6)	1,079 (70.0)	1,093 (71.6)
Did not complete treatment	1,777 (28.9)	491 (31.9)	390 (25.4)	462 (30.0)	434 (28.4)
Reason for early cessation					
Progression	489 (8.0)	151 (9.8)	104 (6.8)	130 (8.4)	104 (6.8)
Death	68 (1.1)	21 (1.4)	16 (1.0)	11 (0.7)	20 (1.3)
Reason other than death or progression	1,162 (18.9)	261 (16.9)	270 (17.6)	321 (20.8)	310 (20.3)
AE	961 (15.6)	208 (13.5)	228 (14.9)	275 (17.8)	250 (16.4)
Other/unknown	201 (3.3)	53 (3.4)	42 (2.7)	46 (3.0)	60 (3.9)
Selective crossover*	58 (0.9)	58 (3.8)	—	—	—
Compliance, No. (%) drug packs†					
Compliant‡	48,593 (94.9)	12,018 (94.4)	12,488 (95.5)	12,032 (94.8)	12,055 (94.8)
Noncompliant					
Stopped drug pack early	750 (1.5)	181 (1.4)	169 (1.3)	200 (1.6)	200 (1.6)
Interrupted for at least 1 week	628 (1.2)	172 (1.4)	141 (1.1)	171 (1.3)	144 (1.1)
Not taken at all	974 (1.9)	288 (2.3)	204 (1.6)	231 (1.8)	251 (2.0)
Other/unknown	273 (0.5)	73 (0.6)	69 (0.5)	60 (0.5)	71 (0.6)
Total drug packs	51,218	12,732	13,071	12,694	12,721

Abbreviations: AE, adverse event; Let, letrozole; Tam, tamoxifen.

*Of 612 women in the Tam arm with selective crossover, 58 had total time on endocrine treatment < 54 months.

†Each drug pack contained a 6-month supply of protocol therapy.

‡At least 80% of doses taken for a drug pack and no interruptions longer than 1 week.

a DFS event. HR was 1.35 (CI, 1.02 to 1.79) using a simple weighted Cox model (Wald χ^2 P = .04) and 1.45 (CI, 1.09 to 1.93) using a multivariable weighted model (Wald χ^2 P = .01).

Sequential therapy: tamoxifen-letrozole and letrozole-tamoxifen. Consistent with the results of the letrozole monotherapy, the analysis of sequential treatments indicated that patients stopping treatment early had worse DFS than those who did not. The relative effect of treatment persistence was approximately the same for both sequences. The HRs of DFS (stopped early *v* not) in tamoxifen-letrozole were 1.46 (CI, 1.13 to 1.88) for the simple weighted model and 1.56 (CI, 1.21 to 2.01) for the multivariable model; in letrozole-tamoxifen, the HRs were 1.46 (CI, 1.12 to 1.87) and 1.57 (CI, 1.21 to 2.03) for the simple and multivariable models, respectively. (Fig 2)

Treatment Compliance and DFS

There were 51,218 drug-pack records in the database; 273 (0.5%) had missing compliance information (Table 1). Figure 3 summarizes the distribution of DFS events according to the compliance score dichotomized at 90%. Results from the Cox regression model show that among women who completed study therapy, there was a statistically significant 61% increase in the risk of a future DFS event for a compliance score of < 90% (HR, 1.61; CI, 1.08 to 2.38; P = .02).

Early Discontinuation and AEs

Early cessation of treatment for reasons other than death or disease progression was documented in 1,162 (18.9%) patients. Of these, 961 stopped early because of AEs (Table 1). Mean treatment duration for those who stopped early because of AEs was 19 months. The cumulative incidence of treatment discontinuation due to AEs is shown in Fig 4. Differences according to treatment assignment were statistically significant (Gray's test P = .009). Letrozole-containing treatments had comparable rates of discontinuation up to 2 years, after which the discontinuation rates in the sequential arms increased. After the treatment switch, patients on the sequential arms were more likely to stop treatment early because of AEs (Table 1; Fig 3). Switching from tamoxifen to letrozole had the highest discontinuation rate (17.9% by 5 years); patients assigned to tamoxifen monotherapy had the lowest (13.6% by 5 years).

Arthralgia was the most common reason for ceasing treatment on letrozole (33%); for tamoxifen, thromboembolic complications were the most common (19%). For the sequential treatments, some AEs (hot flushes and acute illness) leading to cessation were more common with the first drug. For other AEs, cessation was more common on one drug than the other, regardless of whether it was first or second in the sequence (arthralgia/myalgia and gastrointestinal AEs for letrozole and thromboembolic complications for tamoxifen; Fig 5).

Predictors of Early Treatment Discontinuation Due to AEs

Competing risks regression identified five factors that were significantly associated with increased likelihood of stopping treatment early due to AEs: older age, current/previous smoking, node-negative status, prior history of thromboembolic event, and sequential treatment assignment (Table 2).

Fig 2. Unadjusted Anderson-Simon-Makuch survival estimates of disease-free survival (DFS) comparing patients (Pts) who received ≥ 36 months of assigned endocrine treatment (blue line) with those who received < 36 months (gold line) for patients assigned to (A) letrozole (Let), (B) tamoxifen (Tam) for 2 years followed by Let for 3 years, and (C) Let for 2 years followed by Tam for 3 years.

Fig 3. Conditional landmark (54 months) disease-free survival (DFS) comparisons of patients (Pts) who received at least 54 months of protocol-assigned endocrine treatment according to the compliance score dichotomized at 90%. Results from the Cox regression model show a statistically significant 61% increase in the risk of a future DFS event for treatment completers if less than 90% of the drug packs were taken per protocol. HR, hazard ratio.

DISCUSSION

This analysis of BIG 1-98 is the first to report the association between adherence and DFS in the setting of a large adjuvant therapy trial. It provides separate evaluations of both components

of adherence, persistence and compliance, and their relationship to patient outcome. In this analysis, reduced persistence and reduced compliance were both associated with statistically significant increases in the risk of a DFS event.

Because others have shown that longer durations of adjuvant tamoxifen result in superior outcomes,^{4,9-11} it is not surprising that patients in the BIG 1-98 trial who ceased protocol-assigned endocrine treatment before completion experienced an increased risk of a DFS event. What is of interest is the magnitude of the increase (35% to 56%) imparted by reduced persistence. The results of this analysis also suggest that a reduction in compliance translates into a DFS disadvantage, and it is the first to show that breast cancer outcomes relate to daily tablet compliance. Previous studies have largely evaluated persistence or a combination of persistence and compliance.^{12,13,28,29}

The frequency and reasons for discontinuation in the current analysis are consistent with those of other trials in similar settings. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) and Intergroup Exemestane Study (IES) studies, discontinuation ranged from 8% to 15%.^{30,31} On the other hand, the rates of discontinuation reported in BIG 1-98 are generally less than those reported in studies of endocrine treatment discontinuation in the general breast cancer population.^{29,32-42} A recent systematic review identified 29 studies of adjuvant endocrine treatment adherence: compliance ranged from 41% to 72% and persistence from 31% to 73%.²⁹ This disparity suggests that clinical trial participants differ from the general population and are perhaps influenced by factors such as higher motivation, better support, and reduced treatment costs. Several small studies have suggested that information and support interventions improve adherence, lending credence to this possibility.⁴³⁻⁴⁵

The current analysis demonstrates significant differences in early discontinuation according to treatment arm, with greatest persistence associated with the tamoxifen monotherapy arm (86.9%) and least with the tamoxifen followed by letrozole arm (79.8%). Discontinuation rates are comparable for all treatments until 24 months; thereafter, discontinuation was higher in the sequential arms after therapy changed. This observation is especially noteworthy because letrozole-containing treatments remained blinded throughout the trial.

Contrary to our results, some previous studies demonstrated equivalent adherence to AIs and tamoxifen,¹⁷ and a recent review²⁸ noted better adherence with AIs in the large randomized adjuvant and prevention trials. But, as seen here, other studies have demonstrated reduced adherence to sequential treatments. More patients in the IES,³¹ Arimidex-Nolvadex (ARNO) 95, and Austrian Breast Cancer Study Group (ABCSG) studies^{46,47} were adherent to tamoxifen continuation than to a switch to an AI, and a similar pattern is seen in clinical practice.^{15,39,48} Furthermore, in a systematic review of 30 studies of adherence to adjuvant hormonal therapy in clinical practice, Murphy et al²⁹ found only two statistically significant predictors of early discontinuation—switching treatment and high CYP2D6 levels.

Previous analyses of BIG 1-98 have shown that letrozole followed by tamoxifen has similar DFS to letrozole monotherapy, that tamoxifen followed by letrozole could be an appropriate option for lower-risk patients,⁶ and that sequenced treatment may be an appropriate option for some patients.⁴⁹ However, the higher

Fig 4. Cumulative incidence of stopping protocol-assigned endocrine treatment because of an adverse event according to treatment assigned in the Breast International Group 1-98 clinical trial. The sequential treatment (gray and red lines) had the highest incidence of stopping early after the endocrine agent switch at 2 years. Tamoxifen (Tam; blue line) continued to have lowest incidence of stopping early. Let, letrozole.

Fig 5. Adverse events reported as reason for stopping protocol-assigned endocrine treatment early according to treatment group. Let, letrozole; Tam, tamoxifen.

rates of discontinuation for sequential treatments suggest that patients may find it easier to handle consistency in AEs rather than a change. The switch from tamoxifen to letrozole seems particularly troublesome, largely because of arthralgia. Five years of an AI is generally considered the most appropriate strategy for higher-risk patients,⁵⁰ and better adherence to monotherapy, versus a sequenced approach as seen in our study, further supports this strategy.

AEs are the most common reason recorded for early discontinuation and for reduced day-to-day compliance in BIG 1-98. Several,^{42,51} but not all,³⁵ previous studies demonstrate similar discontinuation rates due to AEs. The AEs leading to discontinuation in BIG 1-98 vary according to the treatment and

reflect the most significant AEs reported by patients in AI and tamoxifen trials^{27,28,38,39,44-48}; musculoskeletal and thromboembolic and/or vasomotor, respectively, consistent with a study by Henry et al,⁵² where 24% of 500 patients randomly assigned to letrozole or exemestane discontinued treatment because of arthralgia.

A limitation of this study is the potential for bias due to the heterogeneity of patients who were, or were not, adherent. We have addressed this issue using MSM. An acknowledged limitation of MSM is the necessity of making assumptions that may not be verifiable from the clinical trial data. It was necessary for us to assume that the decision to stop study treatment early could be completely described by the patient's demographic, disease, and treatment characteristics and by high-grade or other serious AEs that occurred during therapy. Other limitations include retrospective drug-pack data collection for some patients, that reasons for treatment cessation were not always reported, and well-documented difficulties in measuring adherence.¹⁹

In conclusion, this analysis shows that both components of adherence, persistence and compliance, are associated with DFS. Nearly one in five patients discontinued treatment before a disease event, largely because of AEs. The sequential treatment arms were associated with the highest rates of reduced persistence. These results reinforce the importance of optimizing adherence by educating and supporting patients about the prognostic importance of adherence, the possible AEs associated with switching treatment, and effective toxicity management.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

Table 2. Baseline Patient, Disease, Treatment Factors Related to Stopping Protocol-Assigned Treatment Early Because of Adverse Events

Factor	HR	95% Wald Confidence Limits		P
Age group, years				
56-70 v ≤ 55	1.022	0.871	1.200	< .001
70 or older v ≤ 55	1.478	1.196	1.826	.78
Nodal status				
N positive v Nx/N0/missing	0.827	0.717	0.954	.009
Nx/N0/missing v N positive	1.209	1.048	1.395	.009
Smoking status				
Former v current	0.939	0.770	1.145	.003
Missing v current	0.763	0.425	1.369	.53
Never v current	0.755	0.639	0.893	.36
Treatment assignment				
Let v Tam	1.046	0.867	1.263	.001
Tam-Let v Tam	1.288	1.076	1.543	.006
Let-Tam v Tam	1.177	0.979	1.415	.02
Tam-Let v Let	1.231	1.033	1.468	.19
Let-Tam v Let	1.125	0.940	1.346	
History of thromboembolic event				
Yes v no	1.415	1.044	1.918	.02

Abbreviations: Let, letrozole; Nx, lymph nodes not assessed; Tam, tamoxifen.

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Treatment Adherence and Its Impact on Disease-Free Survival in the Breast International Group 1-98 Trial of Tamoxifen and Letrozole, Alone and in Sequence

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Acknowledgment

We thank the patients, physicians, nurses, and data managers who participated in the BIG 1-98 clinical trial.

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