Adherence to adjuvant endocrine therapy in estrogen receptor–positive breast cancer patients with regular follow-up

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Background: Adjuvant hormonal therapy is crucial in the treatment of estrogen receptor–positive breast cancer. The nonadherence rate to hormonal treatment is reported to be as high as 60%. The goal of this study was to evaluate the factors evoked by the patients as well as the demographic and disease-related factors that could be associated with nonadherence to adjuvant hormonal therapy.

Methods: All consecutive patients treated for an estrogen receptor–positive breast cancer who showed up for regular follow-up with a single breast specialist between November 2008 and April 2009 were included in the study. We assessed adherence to hormonal therapy (either with tamoxifen or aromatase inhibitor). Reasons for adherence and nonadherence were collected. Records were also reviewed for demographic and cancer characteristics and for treatment components.

Results: We included 161 patients in the study; 150 (93.2%) adhered to hormonal treatment. Side effects and absence of conviction were the main reasons for nonadherence. The importance of the diagnosis of cancer, fear of recurrence and regular follow-up were reported as the main reasons for adherence.

Conclusion: Severity of disease and side effects are associated with nonadherence to treatment. Strict follow-up appears to be a necessary adjunct in the adherence to treatment. The association between demographic and cancer characteristics and treatment components needs further investigation. However, these factors may help identify patients at risk of nonadherence and help the oncology team.

Contexte : Le traitement hormonal adjuvant est crucial dans le traitement du cancer du sein avec récepteurs estrogéniques positifs. Le taux d'inobservance au traitement hormonal atteint 60 %. Le but de cette étude consiste à évaluer les facteurs évoqués par les patientes ainsi que les facteurs démographiques et pathologiques pouvant être associés à l'inobservance au traitement hormonal adjuvant.

Méthodes : Toutes les patientes qui ont été traitées pour cancer du sein avec récepteurs estrogéniques positifs et suivies régulièrement par un spécialiste du cancer du sein de novembre 2008 à avril 2009 ont été incluses dans l'étude. L'adhérence au traitement hormonal (tamoxifène ou inhibiteur de l'aromatase) a été évaluée. Les dossiers des patientes ont aussi été révisés pour colliger les facteurs démographiques, pathologiques et thérapeutiques.

Résultats : Il y a eu 161 patientes; 150 (93,2%) ont suivi le traitement hormonal. Les effets secondaires et l'absence de conviction des patientes face au bénéfice du traitement furent les principales raisons évoquées pour ne pas prendre la médication. L'importance du diagnostic de cancer, la peur de récidive et le suivi régulier furent les principales raisons rapportées pour suivre le traitement.

Conclusion : La sévérité de la maladie et les effets secondaires sont associés avec l'inobservance au traitement hormonal. Le suivi rigoureux semble s'avérer nécessaire dans l'observance au traitement des patientes. La relation entre les facteurs démographiques, les caractéristiques du cancer et du traitement nécessite une investigation plus approfondie. Cependant, ces facteurs peuvent certainement permettre d'identifier les patientes à risque d'inobservance et aider l'équipe d'oncologie à optimiser les discussions.

Breast cancer is the most common newly diagnosed cancer worldwide in women, mostly postmenopausal women,[1–3] and the incidence is increasing.[4] Even if adjuvant therapy with tamoxifen has been challenged by the advent of aromatase inhibitors,[5–17] hormonal therapy remains the

standard of care in the treatment of women with hormone receptor–positive breast cancer.[18–20] Decreased survival is associated with noncompliance with adjuvant hormonal treatment.[18,21] Tamoxifen has been proven to provide substantial reduction in relapses and death in both node-negative[18,22] and node-positive[18] patients. Results of studies using aromatase inhibitors[9,12,16] reinforced the benefit of endocrine adjuvant therapy.[23]

Noncompliance with adjuvant hormonal therapy is an underappreciated, underreported issue[24–26] and is difficult to assess in clinical practice.[27] The problem of nonadherence to hormonal treatment is estimated to be between 30% and 60%[20,23,24,28–32] and may increase with time.[32,33] As many as 50% of all prescriptions may go unfilled.[23,32] Partridge and colleagues[33] showed that 13% of patients fill their prescriptions less than 80% of the time during the first year and that this proportion increases to 80% during the fourth year. In clinical trials, a non-negligible rate of nonadherence to hormonal therapy has been demonstrated,[23,27,28,33–36] even in a setting that is considered ideal for the promotion of adherence to treatment.[23] In the NSABP B-14 trial, which evaluated adjuvant tamoxifen therapy in women with node-negative, estrogen receptor–positive breast cancer, 23% of patients treated with either tamoxifen or placebo discontinued treatment during the 5 years of scheduled therapy.[37] The INT-0102 protocol, which evaluated 2 regimens of chemotherapy alone or in combination with tamoxifen showed a 36% rate of discontinuation of the associated hormonal therapy.[22] Overall, it is estimated that about 25% of the population studied in clinical trials are nonadherent or discontinue treatment.[38] Since findings from clinical trials are believed not to reflect what happens in clinical practice,[27] the "real-life" problem of nonadherence is more important than actually thought.

Many factors have been suggested as predictors of nonadherence to hormonal treatment, demographic (age, race, comorbidities, cognitive impairment) and disease-related factors (type of surgery, chemotherapy, side effects, nodal status).[20,24,27,32] These factors, although significantly associated with nonadherence to hormonal treatment, seem not to completely explain the complex concept of compliance.[23] Psychological factors, such as beliefs, perception, education, source and quality of information, social support) are also suggested to contribute to nonadherence,[20,24,27,28,32–35,39] but studies are inconsistent and the methodologies present important limitations.[32] Suggested solutions include patient education by physicians and nurses[23,28,35] through regular follow-up,[27,28,35] but results remain unconvincing.[23]

The first goal of the present study was to qualitatively evaluate the adherence to hormonal therapy in a sample of patients who had regular follow-up visits with a breast specialist. The second goal was to quantitatively assess factors associated with nonadherence to treatment in this setting.

METHODS

All consecutive patients scheduled for regular follow-up with a single breast specialist from November 2008 to April 2009 were considered for the study. Patients were included in the study if they had been treated for an estrogen receptor–positive breast cancer with tamoxifen or aromatase inhibitor in the previous 10 years. The patients were informed of the study at the time of their visit. All patients underwent a 30-minute interview conducted by a reasearch assistant (K.B.) at the same time as a follow-up visit with their physician. The interviews focused on adherence or nonadherence to hormonal therapy, the perceptions of the patients about the beneficial or nonbeneficial aspects of the treatments and the reasons for adhere or nonadherence to treatment.

Specifically, patients were asked
- "Did/do you take all your pills for the treatment of your breast cancer?"
- "How many times did you forget or omit your pills?"
- "If you omitted your pills, what were/are the reasons?"
- "If you chose/choose not to take or to stop the hormonal treatment, what were/are the reasons?"
- "If you took/take your hormonal treatment, what were/are the reasons?"

Patients were then allowed to spontaneously expand on their answers. Conversations were written down and analyzed at the end of the study period.

Complete adherence to treatment was defined as 100% medication intake, as reported by the patient. It was not possible to review pharmacy records for the entire duration of the study period, but copies of prescriptions were available in the patients' records. Acceptable adherence was defined as 80% medication intake. We reviewed the patients' records for demographics, cancer characteristics and treatment components.

Statistical analysis

We performed univariate and multivariate analyses using 100% adherence and 80% adherence as dependent variables. To build the final predictive models, factors with a significance level of $p \leq 0.20$ in either the univariate or the multivariate analysis were entered. We used the Hosmer–Lemeshow (HL) statistic to evaluate calibration of the models, and the area under the receiver operating curve (AUC) was used to evaluate discrimination.

RESULTS

During the study period, 398 women with 401 breast cancers were scheduled for regular follow-up. There were 190 patients with hormone receptor–positive cancer, defined as positive estrogen/progesterone receptors in more than 10% of cells. Of these patients, 29 were excluded for

the following reasons: hormonal treatment started more than 10 years before the start of the study period (*n* = 14), loss to follow-up (*n* = 10) or inadequate interview and follow-up data (*n* = 5).

Our final study population included 161 women with a mean age of 56.6 (range 29–84) years. Table 1 summarizes the demographic factors, cancer characteristics and treatment components of study participants. There were 46 (28.6%) patients younger than 50 years, 98 (60.9%) aged 50–69 years and 17 (10.6%) aged 70 years or older. At the time of diagnosis, 111 (68.9%) patients were in menopause. Nineteen (11.8%) patients received preoperative neoadjuvant therapy and 60 (37.3%) received postoperative chemotherapy. Tamoxifen was prescribed for 94 (58.4%) patients and aromatase inhibitors were prescribed for 105 (65.2%); 36 (22.3%) patients received both regimens at different points during their treatment. A rate of 100% adherence was reported in 80.7% of patients: 77.6% for tamoxifen and 79.6% for aromatase inhibitors, and a rate of 80% adherence was reported in 93.2% of

patients: 90.4% for tamoxifen and 93.3% for aromatase inhibitors.

Total mastectomy was carried out in 31 (19.3%) patients and formal axillary dissection in 91 (56.5%) patients. Most women received surgery before the implementation of routine sentinel node biopsies. Postsurgery tumour status was T0 in 19 (11.8%) patients, T1 in 100 (62.1%), T2 in 33 (20.5%), T3 in 5 (3.1%) and T4 in 4 (2.5%). Positive nodes were found in 57 patients (35.4%). Of the 140 women for whom a HER2-neu marker analysis was available, 23 (16.4%) were found to have this marker. Hormone replacement therapy was underway at the time of the interview in 59 (36.6%) patients. Chronic medication intake for comorbidities was concomitant in 29 (18.0%) patients.

Table 2 shows the nonadjusted and adjusted odd ratios. In patients with 100% adherence to treatment, N2 nodal status, HER2-neu positivity, hormone replacement therapy and chronic medication intake were significant predictors of nonadherence in the univariate analysis; only previous hormone

Table 1. Distribution of factors in groups of adherence					
		Group; %*			
		100% adherence		80% adherence	
Factor	Total; No. (%)* *n* = 166	Yes, *n* = 130	No, *n* = 31	Yes, *n* = 150	No, *n* = 11
Age, mean ± SD yr	56.6 ± 10.6	57.4 ± 10.9	53.1 ± 8.6	57.0 ± 10.6	52.0 ± 9.3
29–49	46				
50–69	98				
70+	17				
Menopause	111 (68.9)	71.5	58.1	68.7	72.7
Neoadjuvant therapy	19 (11.8)	13.1	6.5	12.0	9.1
Postoperative chemotherapy	60 (37.3)	33.8	51.6	35.3	63.6
Tamoxifen	94 (58.4)	56.2	67.7	56.7	81.8
Aromatase inhibitor	105 (65.2)	62.3	77.4	65.3	63.6
Tumour status					
T0	19 (11.8)	12.3	9.7	12.0	9.1
T1	100 (62.1)	62.3	67.7	62.7	72.7
T2	33 (20.5)	20.0	16.1	20.0	9.1
T3	5 (3.1)	3.1	3.2	2.7	9.1
T4	4 (2.5)	2.3	3.2	2.7	0.0
Node status					
N0	104 (64.6)	66.2	51.7	63.1	70.0
N1	43 (26.7)	26.9	31.0	28.9	10.0
N2	13 (8.1)	6.2	17.2	7.4	20.0
N3	1 (0.6)	0.8	0.0	0.7	0.0
HER2-neu positive, *n* = 140	23 (16.4)	12.4	33.3	12.4	63.6
Partial mastectomy	130 (80.7)	81.5	77.4	80.7	81.8
Total mastectomy	31 (19.3)	18.5	22.6	19.3	18.2
Axillary dissection	91 (56.5)	56.9	54.8	56.7	54.5
Hormone replacement therapy	59 (36.6)	41.5	16.1	38.0	18.2
Patient's history of cancer	9 (5.6)	6.9	0.0	6.0	9.1
Family history of cancer	16 (9.9)	10.8	6.5	10.7	9.1
Family history of breast cancer	52 (32.3)	35.2	23.3	32.7	27.3
Other chronic medication	29 (18.0)	21.5	3.2	19.3	9.1

SD = standard deviation.
*Unless otherwise indicated.

replacement therapy was significantly associated with nonadherence to treatment in the multivariate analysis. The final model includes menopause at the time of diagnosis, aromatase inhibitor therapy, nodal status, HER2-neu positivity and hormone replacement therapy (HL_8 = 3.416, p = 0.91; AUC = 0.734, 95% confidence interval [CI] 0.629–0.839).

In patients with 80% adherence to treatment, HER2-neu positivity was a significant predictor of nonadherence in univariate analysis; the use of postoperative chemotherapy and the presence of the HER2-neu marker were significantly associated with nonadherence to treatment in multivariate analysis. The final model included menopause, axillary dissection, postoperative chemotherapy, HER2-neu positivity and hormone replacement therapy (HL_8 = 35.431, p = 0.71; AUC = 0.894, 95% CI 0.823–0.964).

The qualitative analysis of interviews revealed the following reasons for failing to reach 100% adherence: omission (usually forgetting; n = 17), side effects (n = 7), absence of conviction in the necessity of treatment (n = 4), financial problems (n = 1), other acute disease (n = 1) and metastatic disease (n = 1). In women with 80% adherence, side effects (n = 5), absence of conviction (n = 3), other disease (n = 1),

metastatic disease (n = 1), and omission (n = 1) were the reasons given for nonadherence to treatment.

In patients with 100% adherence to treatment (n = 130), reasons reported spontaneously for complete adherence were importance of the diagnosis of cancer (n = 130), fear of recurrence (n = 130), regular follow-up and supervision by physician and/or nurse (n = 79), meticulous personality (n = 29), use of helping device (n = 24), other medication intake and/or other medical problems (n = 18), history of any kind of cancer in family and circle (n = 15), working in the medical or paramedical field (n = 11), influence of friends and relatives (n = 6), inclusion in a research project (n = 4), and the presence of young children (n = 4).

Discussion

Hormonal therapy has become a standard of care in the treatment of women with hormone receptor–positive breast cancer.[18–20] Noncompliance with adjuvant hormonal treatment is associated with decreased survival.[9,12,116,8,21,22–24] Noncompliance is an underappreciated and underreported

Table 2. Odds ratio of risk for nonadherence to adjuvant breast cancer therapy				
	100% adherence, OR (95% CI)		80% adherence, OR (95% CI)	
Factor	Univariate	Multivariate	Univariate	Multivariate
Age, yr				
29–49	—	0.572 (0.188–1.736)	—	1.432 (0.218–9.427)
50–69	0.533 (0.233–1.219)	—	1.103 (0.272–4.472)	—
≥ 70	0.159 (0.019–1.321)	—	0.896 (0.087–9.252)	—
Menopause	0.551 (0.245–1.237)	2.882 (0.576–14.409)†	1.217 (0.309–4.784)	8.377 (0.745–94.218)†
Neoadjuvant therapy	0.458 (0.100–2.098)	0.468 (0.080–2.731)	0.733 (0.089–6.072)	1.993 (0.115–34.695)
Postoperative chemotherapy	2.085 (0.944–4.606)	1.352 (0.385–4.746)	3.203 (0.897–11.442)	31.970 (1.514–674)*†
Tamoxifen	1.640 (0.716–3.756)	2.390 (0.609–9.375)	3.441 (0.719–16.472)	3.210 (0.407–25.29)
Aromatase inhibitor	2.074 (0.832–5.171)	3.935 (0.879–17.613)†	0.929 (0.260–3.319)	0.582 (0.066–5.130)
Tumour status				
T0	—	0.657 (0.285–1.515)	—	0.388 (0.054–2.813)
T1	1.383 (0.368–5.193)	—	1.532 (0.180–13.009)	—
T2	1.026 (0.215–4.886)	—	0.600 (0.035–10.195)	—
T3	1.333 (0.108–16.480)	—	4.500 (0.229–88.243)	—
T4	1.778 (–0.135–23.399)	—	—	—
Node status				
N0	—	1.997 (0.894–4.460)†	—	1.084 (0.256–4.581)
N1	1.474 (0.590–3.681)	—	0.312 (0.037–2.618)	—
N2	3.583 (1.032–12.441)*	—	2.442 (0.450–13.246)	—
N3	—	—	—	—
HER2-neu positive	3.536 (1.332–9.387)*	3.006 (0.913–9.901)†	12.359 (3.251–46.983)*	9.190 (1.608–52.52)*†
Total mastectomy	1.288 (0.498–3.336)	1.670 (0.415–6.718)	0.927 (0.190–4.523)	0.434 (0.031–6.104)
Axillary dissection	0.919 (0.418–2.021)	0.463 (0.124–1.726)	0.918 (0.268–3.139)	0.148 (0.011–2.056)†
Hormone replacement therapy	0.271 (0.098–0.750)*	0.223 (0.060–0.827)*†	0.363 (0.076–1.738)	0.093 (0.008–1.113)†
Patient's history of cancer	0.448 (0.055–3.675)	0.001 (0–1000)	1.567 (0.180–13.629)	0.001 (0–1000)
Family history of cancer	0.571 (0.123–2.656)	0.971 (0.170–5.564)	0.838 (0.101–6.977)	0.001 (0–1000)
Family history of breast cancer	0.561 (0.224–1.409)	0.600 (0.190–1.897)	0.773 (0.196–3.042)	0.582 (0.057–4.999)
Other chronic medication	0.121 (0.016–0.930)*	0.284 (0.033–2.433)	0.417 (0.051–3.391)	0.001 (0–100)

CI = confidence interval; OR = odds ratio.
*p < 0.05.
†Variables included in the final model (p ≤ 0.20).

problem, reaching rates as high as 60%,[20,23,24,28–32] and places patients at risk of inadequate clinical benefit.[24–27,40,41]

The primary goal of the present study was to evaluate the compliance of patients with breast cancer with hormonal therapy when treatment involved regular follow-up with a breast specialist. Although the literature remains scarce concerning the contribution of the required type of follow-up, the need to provide information to the patients remains crucial.[23,42,43] We intended neither to compare type or place for follow-up nor to evaluate the necessity of follow-up by a breast specialist. Only patients who showed up for regular follow-up composed the study population. A selection bias certainly exists, but only a few patients who were given regular appointments did not respect the schedule or were lost to follow-up. Only 8.5% of the maximum of patients that could be included are missing. We did not intend to compare patients with and without follow-up; however, more than 60% of highly compliant patients reported the importance of follow-up in their adherence to therapy.

The fact that 93% of women in our study reported adherence rates of 80% represents a fairly good compliance compared with rates reported in the literature. We considered 100% adherence to treatment to be ideal,[1] but we tolerated 80% adherence as an acceptable threshold.[1,32,42,44] Self-reported rates of adherence have been demonstrated to be higher than rates validated by other means (e.g., pill count, medication possession ratio, electronic means, pharmacy documentation).[23,32,42,45] However, we were quite strict in estimating the probability that patients were taking pills as reported. When in doubt regarding patients who had records with missing prescriptions, gave evasive answers or reported more than occasional omissions of pills, we preferred to consider the patients as nonadherent to treatment.

Patients were allowed to expand on their reasons for adherence or nonadherence to treatments without any suggestions of answers fron the interviewer. Self-reported adherence to treatment tends to overestimate the reality,[25] and our results were certainly no exception. However, because the patients included in the present study adhered to regular follow-up, we remain confident that their self-reported adherence was reasonably honest. Although selection bias remains unavoidable, the patients' adherence to follow-up suggests that the women in our study probably reported a fairly reliable pattern of pill intake. We are also confident in that, even if there could be doubt between complete (100%) and not so complete adherence, no doubt exists between acceptable adherence (80%) and no adherence (< 80%). Since patients spontaneously mentioned barriers to taking pills, the inherent bias of self-reporting must be attenuated, particularly in patients who reported adherence more than 80% of the time. At worse, those who reported taking pills 100% of the time may be reasonably considered as having an acceptable compliance of more than 80%.

Beliefs of patients have been shown to be predictive factors of adherence.[46,47] The patients spontaneously and consistently emphasized the diagnosis of a cancer and the fear of recurrence as reasons for adherence. We feel that this fear of cancer compared with other chronic diseases is a more favourable factor in the patients' incentive for adherence to treatments.[27] However, the importance of information to the patients remains a crucial adjunct because a large proportion also rely on regular follow-up. This correlates with the current literature emphasizing the importance of discussion with physicians.[28,35,48,49]

Among patients with poor (< 80%) adherence, the reasons were generally straightforward: side effects (in half the cases), absence of conviction and other serious problems. It is important to identify the factors reported by nonadherent patients in order to adapt patient education; however, it seems difficult to convince these patients of the benefits of the adjuvant therapy.

There was no statistical association in our study between age and adherence to hormonal treatment. The literature generally shows that younger patients are less compliant with tamoxifen use.[24,28,33] However, younger age and very old age were reported to be associated with significantly less compliance to treatment: ages 25–44 and 75 and older, respectively in 1 study[20] and younger than 45 and 85 and older, respectively, in another study.[35] Our results do not corroborate those reported in the literature, as in the present study the highest level of compliance was observed in patients aged 70 years and older, although this result was not significant. Postmenopausal patients were less compliant with treatment. The reasons for this observation were not clear, but most patients in our study were in an early stage of menopause, and these patients are considered to be young nowadays.

No single factor could identify a patient at risk for nonadherence to treatment, but it is interesting that some factors related with more severe disease were significantly associated with decreased adherence to treatment. Aromatase inhibitor therapy, postoperative chemotherapy, node status, formal axillary dissection and presence of the HER2-neu marker may all imply more severe disease and may affect perception of patients (Table 2). Similar to other authors,[27] we have no explanation for this finding. It is possible that the presence of factors related to more severe disease, such as the presence of the HER2-neu marker, can reinforce a pessimistic attitude and defeatism in these patients. It is important for physicians to have a good relationship with their patients and get a feel for the patient's personality to be able to orient the discussion positively and potentially counteract news that could be improperly interpreted.

Limitations

This study has many limitations. The selection bias of patients who are compliant with their follow-up has

already been addressed. A favourable bias toward the interviewer may have contributed to some overestimation of compliance. In that sense, we agree that the 100% adherence rate to treatment may be overestimated, but we remain confident when we estimated the 80% adherence rate, although there is no basic evidence in the literature to support this assertion.[23,32,42,45] The convenience sample that composed the study population is a limitation of the methodology.

One goal of our study was to evaluate patients in the setting of strict follow-up, and because all patients with diagnosed breast cancer were entered in a database that automated follow-up with the breast specialist, we were able to enrol most eligible patients in our study. Even if our goal was not to evaluate compliance with follow-up, our results suggest a high compliance rate with medication if follow-up is respected. Assigned follow-up, either with the treating physician or alternative members of the health care team (e.g., nurse, oncology team, family doctor) is essential.

Another limitation to our study was the relatively small sample size, although other studies that used interviews in their methodology generally recruited a comparable number of patients.[23,28,42] Larger studies, on the other hand, often failed to address reasons for discontinuation of treatment.[5,24,32] In addition, our study had no control group, but our results were well under the rates of nonadherence in the literature, which have been reported to be as high as 60%.[20,23,24,28–32] Reported adherence in large studies, such as the National Surgical Adjuvant Breast and Bowel Project, was also lower.[19,37] Studies that group the clientele of many physicians probably reflect a mix of personality of the physicians, which could not be addressed in the present study.

Patients need information about breast cancer, the stage of their disease and the reasons for the adjuvant treatment. The fear of cancer and recurrence, a constantly reported reason for treatment adherence in the present study, should be the catalyst for the treating team tailoring their approach with these patients. The risk factors of noncompliance that we identified should help to identify the patients at risk of nonadherence to treatment as well as the factors that could significantly improve adherence. An interview that allows the patients to freely discuss their perceptions, beliefs and plans is, in our point of view, a crucial step in the initial approach by the physician.

Conclusion

Patients with breast cancer who are seen regularly in follow-up visits have an excellent rate of adherence to hormonal treatment. Fear of cancer and recurrence and importance of follow-up are important factors to identify during an interview. Factors of adverse prognosis have the potential to discourage patients from adhering to adjuvant treatment and must be identified and discussed accordingly.

Other studies should confirm the observations and conclusions of this study.

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