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CLINICAL TRIAL

Compliance and persistence of endocrine adjuvant breast cancer therapy

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Abstract This study evaluates compliance and persistence in adjuvant endocrine breast cancer (BC) therapy by clearly analyzing reasons of therapy cessation by differentiating clinical meaningful situations. In order to illuminate the complex field of personal motivation to therapy, a single institution study with a more individual-based approach might better be suited to provide a detailed case documentation than the more epidemiologic approach of large database studies. An unselected cohort of 698 patients (≤80 years) diagnosed with hormonal receptor-positive BC from 1997 to 2008 at the University Hospital Basel, Switzerland, was analyzed. The term "non-persistence" was exclusively used for patients where the discontinuation of endocrine therapy (ET) could have been modified by more intensive care and improved counseling (e.g., in women who lost faith/motivation to therapy or those who suffered from therapy-related side effects). These cases must be differentiated from cases where therapy cessation was inevitable (e.g., due to recurrent disease or severe intercurrent illness). Out of the 685 patients to whom ET was recommended, 42 patients (6.1%) refused and never began treatment (non-compliance). Women younger than 50 were more likely to be non-compliant ($P < 0.001$). 12.9% of the patients who started therapy were non-persistent to therapy. Patients who were treated by general practitioners tended to be non-persistent more often compared to those treated by oncologists (17.7% vs. 11.3%; $P = 0.07$). The aim of a non-persistence rate between 10 and 15% is realistic when patients are treated by specialized oncologists. Interventions are needed to support patients, particularly the younger ones, to comply with therapy. Efforts should be made to make sure that all physicians, above all general practitioners, who are involved in BC treatment, are provided with current knowledge as to guarantee an optimal patient management.

Keywords Breast cancer · Endocrine therapy · Persistence · Compliance

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Introduction

For three decades, a 5 year treatment has been the standard adjuvant endocrine therapy (ET) for women with hormone receptor (HR)-positive breast cancer (BC). In the last years, the topic area of "compliance/adherence/persistence" to adjuvant endocrine treatment has increasingly become a focus of interest [1–3]. The studies, which evaluated this issue, have reported significantly varying non-persistence/non-compliance rates from 11 to 51% [4–16]. This inconsistent data was born, on the one hand, from different methodological approaches (e.g., differing study cohorts in terms of study period, duration of observation, patients'

age, method of obtaining of information regarding drug intake) and on the other hand because the definitions of "compliance" and "persistence/adherence" were not used uniformly [2]. The majority of authors defined any kind of discontinuation of medication as "non-persistence" and did not report the different reasons for discontinuation [5, 9, 10, 12, 13, 16]. Few authors recorded the follow-up data carefully enough so that patients, who had to stop therapy because metastatic disease occurred during the first 5 years of treatment, were steadily excluded from persistence analysis [6, 8].

According to a previous study on postmenopausal BC patients [8], we defined non-persistence to ET in this study as an intentional action of the patients. Following this principle, situations where the discontinuation of therapy was not chosen but was mandatory (e.g., therapy stop due to local or systemic BC recurrence, death on intercurrent illness, therapy stopped by treating physician due to serious medical reasons) were not defined as "non-persistent."

We placed a great deal of importance on the above-mentioned criteria because non-persistence as an intentional action may be preventable by more intensive care and improved counseling and a certain proportion of these patients may potentially be motivated to maintain therapy [8]. Therefore, if one wants to analyze persistence to medication from a clinician's view, we think that the term "non-persistence" should exclusively be used for patients where the discontinuation of therapy could have been modified and clearly differentiate from cases where therapy stop was inevitable.

According to this essential clinical principle, our study evaluates compliance and persistence of adjuvant endocrine BC therapy.

Patients and methods

Data concerning all patients who had HR-positive non-metastatic invasive BC and who received surgical therapy between 1997 and 2008 at the University Hospital Basel (Basel, Switzerland) form the basis of the current analysis; this data was collected in the institutional prospective relational web-based Basel Breast Cancer Database (BBCD). We restricted analysis to women who were 30–80 years old at initial BC diagnosis. In total, 698 patients met these inclusion criteria. In a first step, we excluded the patients to whom ET was not recommended by the institutional interdisciplinary tumor board ($n = 13$; median age: 55 years, range 45–76 years) from further analysis; the reasons for not to recommend therapy included a low-risk constellation (pT1a/b N0, favorable grading) and/or advanced age with considerable comorbidity. In a second step, the actual entire study cohort ($n = 685$) was divided into three age-dependent subgroups; Group A: 30–49 years ($n = 162$; 23.6%); Group B: 50–64 years ($n = 249$; 36.4%); Group C: 65–80 years ($n = 274$; 40.0%).

The following clinicopathological and treatment data was available for all patients: age at initial diagnosis, histological subtype, grading, estrogen receptor (ER) and progesterone receptor (PR) status, tumor stage according to the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) TNM Classification [17, 18], surgery type and receipt of adjuvant chemotherapy and/or radiation. HER-2/neu status has been routinely assessed for all patients since 2002 and was available for 624 patients (91.4%). Furthermore, we recorded the location of treatment and follow-up of the patients (oncology unit or general practitioner).

The treatment recommendations for all patients were based on the decision of the interdisciplinary tumor board of the University Hospital Basel. As of 1997, adjuvant ET has been the standard recommendation for all HR-positive patients, with few exceptions. All patients received a comprehensive consultation at the departmental oncology unit, during which treatment indication and duration, as well as the potential adverse effects, were extensively discussed. All patients who had surgery at the University Hospital Basel were offered to also have follow-up at our institution. This offer was independent of patient's age and comorbidity/health status.

During follow-up, information concerning the prescribed endocrine agent given and duration of the medication was obtained from the medical record. By doing this, we recorded any change of endocrine agents and the indication for the change (e.g., sequential therapy, extended therapy beyond 5 years of adjuvant therapy, or change due to adverse effects). For the patients who stopped therapy, a particular attention was paid to precisely recording the reasons for modifications and discontinuations. Patients who had no follow-up at our institution were monitored via telephone. Afterward, contact was made with the treating physician to confirm the patients' statements.

We had complete follow-up for 677 patients of our study cohort (98.8%); eight patients (1.2%) were lost to follow-up after a median observation time of 14 months (range 1–25 months); these patients were not considered in the analysis of therapy persistence.

Definition of compliance and persistence

In this study, we defined "compliance" as the readiness to accept a proposed drug; in our particular case, to accept

starting the ET. When the patients started the treatment, we used the term "persistence" and not "adherence" for the further intake of the drug regimen. Persistence is defined as the length of time from initiation to discontinuation of treatment; it is a specific aspect of adherence, which is defined as the extent to which patients take medications as prescribed [5, 19, 20]. As it was the intention of our study to evaluate patients' non-persistence, which in most cases occurs within the first 2 years of therapy [8, 12, 13], we also included patients with an ongoing therapy who took their medication for at least 36 months ($n = 129$; 19.1%) and considered these patients as being persistent to therapy. Patients with ongoing extended therapy >5 years were also considered as having fully completed therapy.

In this study, the following situations where the discontinuation of therapy was not chosen but was mandatory were not defined as being "non-persistent":

- Patients who had to stop therapy due to local or systemic BC recurrence.
- Cases where a physician decided to stop the therapy for serious medical reasons other than BC (e.g., in palliative situation of malignant diseases, dependence on nursing care, and severe dementia).
- Patients who died within the planned 5 years of treatment from intercurrent illness and took the medication shortly before death.

Statistical analysis

The Wilcoxon–Mann–Whitney test was used for comparisons of metric parameters. To identify factors associated with (a) compliance and (b) persistence to therapy, we created univariate logistic models with the two endpoints. Each logistic regression model included one of the following variables: year of the initial diagnosis, patient's age at diagnosis, primary surgical therapy, tumor stage, receipt of previous chemotherapy and/or postoperative radiation, and location of follow-up (the latter only in the non-persistence model). Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were reported. Multivariate logistic regression analysis was also applied when appropriate. All statistical analyses were carried out at 5% level of significance and performed with SPlus software (Version 6.1, Insightful Corporation, Seattle, WA).

Results

The clinicopathological, treatment and follow-up characteristics of the 685 patients in the study are summarized in Tables 1, 2, and 3.

Compliance

In total, 42 patients (6.1%) refused the recommended ET and never began the treatment. Multivariate analysis (Table 4) revealed that patients younger than 50 years ($P < 0.001$), and those who received adjuvant chemotherapy and radiotherapy (each <0.001) were more likely to refuse therapy. There are multifaceted reasons to refuse the recommended ET. According to our experience, a lack of belief in the necessity for the benefit of the therapy and/or fear of therapy-related adverse side effects are the most often named concerns of the patients. Despite the undisputed successes of modern therapy approaches, it appears that a certain percentage of the population have a profound mistrust of an aversion to modern western medicine.

Persistence

Of the 567 patients who initiated ET and had a minimum follow-up time of 36 months, 412 (72.6%) fully completed the targeted therapy. Sixteen patients (2.8%) discontinued the therapy due to death, while 60 patients (10.6%) ceased therapy due to BC recurrence. In six cases (1.1%), the therapy was discontinued by the physician due to serious medical reasons independent from BC and therapy-related adverse effects (advanced age/dementia/need for nursing home care, $n = 2$; incurable malignancy other than BC, $n = 3$; irreversible coma following severe head trauma, $n = 1$).

Seventy-three patients (12.9%) were non-persistent to therapy. The main reasons given by the patients are listed in Table 5. Patients who were 50–64 years old had the lowest non-persistence rates (10.7%); younger women (<50 years) showed with 15.6% the highest rate.

Location of follow-up

Of the 567 patients who received adjuvant ET, 454 (80.1%) were treated in an oncology unit and 113 patients (19.9%) had further follow-up through a general practitioner. Uni- and multivariate analysis showed that patients who were treated by general practitioners tended to be non-persistent more often compared to those treated by oncologists (17.7% vs. 11.3%; $P = 0.07$, Table 4).

Discussion

The studies which have addressed non-persistence/non-adherence to endocrine BC therapy in epidemiological studies [5, 9, 12, 13], in clinical trials [21–24] and in clinical practice settings [4, 6–8, 10, 11, 14–16] reported a considerable range of 11–51%. The great variability of the

Table 1 Clinicopathologic and treatment characteristics of 685 women with hormonal receptor-positive breast cancer

Variable	Group A: 30–49 years[a] $n = 162$ (%)	Group B: 50–64 years[a] $n = 249$ (%)	Group C: 65–80 years[a] $n = 274$ (%)	Entire cohort $n = 685$ (%)
Mean age (years)	43.1	57.7	72.1	59.7
Hormonal receptor status				
ER+ PR+	134 (82.7)	182 (73.1)	194 (70.8)	510 (74.5)
Grading				
G1/G2	124 (76.5)	193 (77.5)	202 (73.7)	519 (75.8)
HER-2 neu status				
Known	151 (93.2)	224 (90.0)	250 (91.2)	625 (91.2)
Positive	22 (14.6)	30 (13.4)	23 (9.2)	75 (12.0)
Histologic subtype				
Ductal invasive	130 (80.2)	182 (73.1)	193 (70.5)	505 (73.7)
Lobular invasive	21 (13.0)	45 (18.1)	59 (21.5)	125 (18.3)
Rare types	11 (6.8)	22 (8.8)	22 (8.0)	55 (8.0)
AJCC/UICC stage[b]				
I	73 (45.0)	123 (49.4)	133 (48.5)	329 (48.0)
II	63 (38.9)	92 (36.9)	105 (38.3)	260 (37.9)
III	26 (16.1)	34 (13.7)	36 (13.2)	96 (14.0)
Type of surgery				
Breast conserving therapy	98 (60.5)	168 (67.5)	162 (59.1)	428 (62.5)
Mastectomy	64 (39.5)	81 (32.5)	112 (40.9)	257 (37.5)
Surgical axillary staging (SLND/ALND)	160 (98.8)	241 (96.8)	264 (96.4)	665 (97.1)
Adjuvant radiotherapy	115 (71.0)	195 (78.3)	177 (64.6)	487 (71.0)
Systemic therapy				
Previous chemotherapy	95 (58.6)	81 (32.5)	25 (9.1)	201 (29.3)
Adjuvant treatment with trastuzumab	6 (3.7)	9 (3.6)	6 (2.2)	21 (3.1)

ER estrogen receptor, *PR* progesterone receptor, *AJCC* American Joint Committee on Cancer, *UICC* International Union Against Cancer, *SLND* sentinel lymph node dissection, *ALND* axillary lymph node dissection

[a] Age at initial breast cancer diagnosis

[b] In 17 patients (Group A: $n = 8$; B: $n = 5$; C: $n = 4$), where neoadjuvant therapy was performed, the ypT and ypN status were used for stage grouping

data can only be adequately interpreted when the basic methods of each study are closely analyzed. Major non-uniformities exist within the current literature, which mean useful insights for a current general population are difficult to apply. Prior studies included selected study cohorts such as insurance claims and locally limited public health data [5, 9, 12, 13] or examined certain subgroups of patients from different BC centers [6–8, 10, 11, 14, 16], they were limited to predominantly geriatric patients [5, 7, 10, 11, 13, 14], they had variable observation periods from 17 months [14] to 5 years [7, 8, 10, 11] and partly analyzed treatment that took place in the 1990s when the indication for therapy did not conform to current guidelines [6, 7, 10, 11, 13, 14]. Furthermore, the information whether a drug was taken or not was assessed by different methods; some authors collected information by medical record review and patient interview [6–8, 10, 14], others analyzed prescription data [5, 9, 11–13, 16].

In this study, we aimed to avoid some of the above-mentioned methodological problems in that we minimized selection bias by analyzing and following all surgically treated patients from 30 to 80 years in a 12-year period in which the currently valid guidelines of treatment recommendations [25] were active. This approach allowed us to outline the percentage of patients who were non-compliant and did not start a recommended ET. Information on non-compliance is rare since clinical trials and studies using clinical practice settings exclusively analyzed patients who had started therapy [4, 6, 7, 10, 14, 15, 21–24]. In prescription analyses, a clear differentiation between non-compliance and non-persistence is not possible since there are a considerable number of patients who receive a

Table 2 Course of adjuvant oral endocrine therapy

	Group A: 30–49 years[a] $n = 162$ (%)	Group B: 50–64 years[a] $n = 249$ (%)	Group C: 65–80 years[a] $n = 274$ (%)	Entire cohort $n = 685$ (%)
Noncompliance				
Patients refused to initiate therapy	19 (11.7)	10 (4.0)	13 (4.7)	42 (6.1)
Lost to follow-up	3 (1.9)	3 (1.2)	2 (0.7)	8 (1.2)
Therapy persistence				
Patients who initiated oral endocrine therapy and had complete (at least 30 months) follow-up[b,c]	122 (100)	215 (100)	230 (100)	567 (100)
I. Therapy completed	103 (84.4)	192 (89.3)	199 (86.5)	494 (87.1)
Therapy fully completed	88 (72.1)	163 (75.8)	161 (70.0)	412 (72.6)
Therapy discontinued due to death	–	5 (2.3)	11 (4.8)	16 (2.8)
Median duration of therapy (range)		23 (9–48) mths	16 (1–48) mths	
Therapy discontinued due to BC recurrence	15 (12.3)	22 (10.2)	23 (10.0)	60 (10.6)
Median duration of therapy (range)	35 (10–55) mths	20.5 (3–45) mths	28 (4–58) mths	
Therapy stopped due to medical reasons independent from BC and therapy-related adverse effects	–	2 (1.0)	4 (1.7)	6 (1.1)
Duration of therapy		28, 39 mths	25 (1–52) mths	
II. Non-persistence	19 (15.6)	23 (10.7)	31 (13.5)	73 (12.9)
Non-persistence due to therapy-related adverse effects	10 (8.2)	15 (7.0)	16 (7.0)	41 (7.2)
Median duration of therapy (range)	19 (2–39) mths	14 (5–46) mths	6 (1–30) mths	
Non-persistence due to other reasons	9 (7.4)	8 (3.7)	15 (6.6)	32 (5.7)
Median duration of therapy (range)	24 (1–47) mths	40 (10–47) mths	30 (1–50) mths	
Location of follow-up				
Oncological unit	105 (86.1)	173 (80.5)	176 (76.5)	454 (80.1)
General practitioner	17 (13.9)	42 (19.5)	54 (23.5)	113 (19.9)

BC breast cancer, *mths* months

[a] Age at initial breast cancer diagnosis

[b] The following number of patients, who were diagnosed during 2008/2009, started oral endocrine therapy but had no follow-up time longer than 36 months at the time of data analysis in April/May 2011 and were therefore not considered in the analysis of therapy persistence: Group A: $n = 17$; Group B: $n = 21$; Group C: $n = 29$

[c] In addition to the patients who were lost to follow-up, one further patient who had GnRH analog therapy only was excluded from analysis

prescription, fill it, read the information and direction for use and then ultimately decide not to start the therapy [5, 9, 11–13].

In our view, non-persistence to therapy is not simply the act of stopping medication, but rather the manifestation of an intentional behavior (with very few exceptions, e.g., patients who stopped therapy due to misinformation by their physicians or those whose ability to continue therapy was impaired by alcohol/drug dependency or psychiatric diseases). The reasons for non-persistence such as distressing adverse effects, inadequate clarification of the benefits of therapy, and fear and mistrust of the agent prescribed, can be elucidated in most cases. An important aspect of non-persistence to treatment is the ability of the treating physician to intervene and change the attitude that led to the discontinuation. We think that studies on persistence and adherence to therapy, which in principle try to illuminate the complex field of personal motivation to therapy, requires a careful and detailed clinical follow-up and a clear discrimination between situations where patients refused the recommended therapy or were non-persistent (whose attitude and behavior may be potentially influenced) and those whose therapy had to be stopped due to BC recurrence or other serious medical reasons (i.e., discontinuation of the therapy was unavoidable). It is a particular strength of our study that we accomplished this clinically relevant innovative approach. The epidemiological studies on this topic [9, 12], which might impress with high patient numbers but could not provide an exact individual-based follow-up, disappointed in this context. We will even take one step further and declare that the studies with the largest number of patients provide the lesser

Table 3 Endocrine therapy regimen

	Group A: 30–49 years[a] $n = 143$ (%)	Group B: 50–64 years[a] $n = 239$ (%)	Group C: 65–80 years[a] $n = 261$ (%)	Entire cohort $n = 643$ (%)
Initial agent prescribed				
Tamoxifen	122 (85.3)	151 (63.2)	168 (64.4)	441 (68.6)
Anastrozole	11 (7.7)	37 (15.5)	49 (18.8)	97 (15.0)
Letrozole	8 (5.6)	34 (14.2)	27 (10.3)	69 (10.7)
Exemestane	1 (0.7)	2 (0.8)	2 (0.8)	5 (0.8)
Study medication (BIG 1–98 trial)	–	15 (6.3)	14 (5.3)	29 (4.5)
GnRH analog alone	1 (0.7)	–	–	1 (0.2)
GnRH analog combined with oral agents	53 (43.1)[b]	2 (0.8)	–	55 (8.6)
Fulvestrant			1 (0.4)	1 (0.2)
Surgical oophorectomy, intended as endocrine therapy	24 (16.8)	2 (0.8)	–	26 (4.0)
Median time from BC diagnosis to ovarian ablation (mths)	41, range 1–90	4.5 (1,9)	–	
Reason of change of the agent prescribed (number of patients)				
Adverse effects (within the first 5 years of therapy)	10	37	37	84
Sequential therapy[c]	15	28	22	65
Extended therapy beyond 5 years	30	36	17	83

BIG Breast International Group, *BC* breast cancer

Endocrine therapy regimen included were all patients who started endocrine therapy; eight patients who were lost to follow-up were not considered

[a] Age at initial breast cancer diagnosis

[b] Combination with tamoxifen, $n = 9$; with anastrozole, $n = 1$; with letrozole, $n = 2$; with exemestane; $n = 1$

[c] Due to medication blinding, switching endocrine therapy within the BIG 1–98 trial was not considered

meaningful clinical insights. We want to comment on this by discussing two studies which analyzed more than 20,000 individuals in total.

(1) The first study, conducted by Partridge et al. [12], aimed to examine 3 year adherence to adjuvant anastrozole therapy using longitudinal claims data from three large commercial health programs. In total, they identified more than 17,000 women who had new anastrazole prescriptions. However, public databases, which record patient data only to the extent that was necessary for administrative statistical purposes, are not able to provide reliable information regarding disease stage, which is an essential cornerstone in any oncological publication and defined inclusion criterion in the study. Disease stage was derived from claims-based staging algorithm. How error-prone this method can be demonstrated by the fact that an unrealistic low percentage of the cohort ($n = 242$; 1.4%) was identified as having advanced BC (i.e., the authors presumably analyzed non-persistence also in patients in the palliative situation). A further 26% could also not be analyzed because the stage was found to be "indeterminate classification." We think it must be questioned whether a data collection, which cannot even give precise information regarding comparably easy to record morphological features (disease stage), can provide solid information concerning the often complex individual clinical situations and reasons that lead to cessation of medication. On the other side, more than 12,000 women, who were assumed to have early BC, would theoretically still have been an interesting cohort with which to study persistence. However, the approach universally disappoints since the authors could give information regarding drug persistence after a 3-year observation period in only 8% ($n = 999$) of the initially analyzed 12,000 women.

(2) Hershman et al. [9] used automated pharmacy records to identify hormonal therapy prescriptions and dates of refill and included 8,769 early-stage BC patients in their analysis. They found that only 49% of patients took ET for the full duration at the optimal schedule. However, this study suffered as well from severe methodological problems. The authors wanted to exclude patients who stopped therapy due to BC recurrence. This is without a doubt a reasonable approach, but they only identified BC recurrence in 5% of their cohort within a 4.5-year period of observation; this, however, is an unrealistic low percentage. Again, one must argue how reliable is a data collection, which fails to record an essential event in the course of BC precisely, with regard to persistence on drug intake, which mirrors individual motivations and life concepts. The authors admitted that there was a limitation to their

Table 4 Univariate and multivariate relationships between potential predictors and non-compliance (a) and non-persistence to therapy (b)

Variable	Univariate calculation		Multivariate calculation	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
a. Non-compliance ($n = 42$)				
Advanced age*	0.34 (0.25–0.48)	0.001*	0.17 (0.12–0.24)	<0.001
Year of the initial diagnosis**	1.08 (1.04–1.13)	0.06	–***	
TNM disease stage[a]: stage I vs. II vs. III	0.54 (0.41–0.69)	0.02	0.87 (0.64–1.17)	0.65
Surgical therapy: BCT vs. mastectomy	0.73 (0.52–1.03)	0.36	–***	
Previous chemotherapy: yes vs. no	5.88 (3.13–11.12)	0.004	12.50 (5.88–20.00)	<0.001
Radiotherapy: yes vs. no	3.22 (2.38–4.54)	<0.001	3.57 (2.58–5.00)	<0.001
b. Non-persistence ($n = 73$)				
Advanced age*	0.68 (0.52–0.91)	0.19	–***	
Year of the initial diagnosis**	1.01 (0.97–1.04)	0.76	–***	
TNM disease stage[a]: stage I vs. II vs. III	0.68 (0.57–0.83)	0.02	0.71 (0.58–0.85)	0.15
Surgical therapy: BCT vs. mastectomy	0.96 (0.74–1.25)	0.88	–***	
Previous chemotherapy: yes vs. no	1.18 (0.88–1.53)	0.58	–***	
Radiotherapy: yes vs. no	1.53 (1.18–2.00)	0.11	–***	0.08
Location of follow-up: general practitioner vs. oncological unit	0.61 (0.46–0.81)	0.004	0.66 (0.49–0.88)	0.07

BCT breast conserving therapy

[a] AJCC (American Joint Committee on Cancer)/UICC (International Union Against Cancer) TNM Classification

* Younger 50 vs. equal older 50; ** less (1997) vs. more recent (2009) diagnosis, continuous variable in step of 1 year

–*** If univariate calculations showed a *P* value >0.5, we did not report multivariate calculation due to statistical insignificance

Table 5 Non-persistence to endocrine therapy: main reasons for and period of discontinuation in 73 non-persistent patients

	Group A: 30–49 years[a] $n = 19$ (%)	Group B: 50–64 years[a] $n = 23$ (%)	Group C: 65–80 years[a] $n = 31$ (%)
Main reasons for discontinuation[b]			
Lack of motivation, resistance against drug intake, wish to stop	7 (28.0)	5 (17.9)	12 (31.6)
Complaints falsely interpreted as therapy-related side affects	–	1 (3.5)	–
Desire to get pregnant	4 (16.0)	–	–
Insurance technicalities	–	1 (3.5)	–
Misinformation by physician	–	–	1 (2.6)
Intolerance, general discomfort, and malaise	3 (12.0)	6 (21.4)	12 (31.6)
Weight gain	2 (8.0)	–	–
Hot flushes	5 (20.0)	7 (25.0)	4 (10.5)
Musculoskeletal events (e.g., arthralgia, bone pain)	2 (8.0)	5 (17.9)	3 (7.9)
Thrombosis/embolism	–	–	1 (2.6)
Hypertension	–	–	2 (5.2)
Dermatologic symptoms/hair loss	1 (4.0)	–	2 (5.2)
Visual disturbances	–	1 (3.5)	1 (2.6)
Alcohol dependency or psychiatric disease	1 (4.0)	2 (7.3)	–
Period of discontinuation (year of therapy)			
First year	6 (31.6)	9 (39.1)	16 (51.6)
Second year	3 (15.8)	4 (17.4)	5 (16.1)
Third year	6 (31.6)	3 (13.1)	4 (12.9)
Fourth year	4 (21.0)	6 (26.1)	4 (12.9)
Fifth year	–	1 (4.3)	2 (6.5)

[a] Age at initial breast cancer diagnosis

[b] In some cases, there were two different main reasons to stop therapy: Group A: $n = 6$; Group B: $n = 5$; Group C: $n = 7$

study by the fact that they were unable to determine the reasons for discontinuation of therapy, but they did not discuss this point further. We think that this point especially deserves a further comment and we want to illustrate this with the following exemplary individual situations and reasons that led to a stop of endocrine BC therapy in practice: (i) a woman who had to stop therapy due to liver metastases, (ii) those where a physician decided to stop therapy because of an incurable pancreatic carcinoma, (iii) those where a physician decided to stop therapy due to a severe dementia, (iv) a young women who preferred to discontinue ET because of the wish to get pregnant, (v) an older woman with considerable comorbidity who wished to reduce the number of her daily drug intake, (vi) those who want to stop therapy because they suffered from hot flushes or arthralgia, (vii) those who lost faith in the necessity of treatment, (viii) those who were just tired of therapy because they did not want to be reminded of their cancer disease every day, (ix) those who stopped therapy sometime during a process of deprivation due to alcohol dependency. This list could easily be extended. No one with any clinical sense could seriously believe that these situations should be categorized in one group. This synonymous use of the terms "discontinuation" and "non-persistence/non-adherence," however, was the practice in most of the studies evaluating persistence/adherence to adjuvant ET [4, 5, 7, 9–14, 16, 26]. We think that analysis of drug persistence implies the readiness to engage with individual histories and to clearly categorize these in clinically meaningful subgroups. If a study misses this approach, their results will hardly give information beyond a market analysis for the pharmaceutical industry.

The limitations of our study, however, must be considered. First, our study relies on information obtained by patients' self-report of persistence. It is possible that in some cases the patients who reported continuing to take medication had indeed stopped taking it and just gave a socially acceptable answer. Furthermore, we could neither consider a non-intentional non-adherence, i.e., the patients just forgot to take their medication [4] nor the fact that self-reported adherence fairly consistently underestimates non-adherence as determined by more objective measures [15, 16].

Our 12.9% rate of non-persistence to adjuvant ET (for the entire cohort) was considerably lower than that reported in most other clinical practice settings (21–51%) [5, 7, 9–13, 16]; these studies, however, were plagued by the previously mentioned methodological weaknesses. With a non-persistence rate of 15% after a 3-year observation period, Demissie et al. had findings most similar to ours [6]. Not surprisingly, they avoided the major methodical shortcoming of other studies in that they excluded patients who stopped therapy due to BC recurrence from the group of non-persistent patients. When compared to the non-persistent rates reported in clinical trials (i.e., withdrawal of study medication), which compared tamoxifen with an aromatase inhibitor (tamoxifen: 11–13%, aromatase inhibitors: approximately 12%) [21, 22, 24], our results appear realistic, particularly when one considers that withdrawal of study medication does not always mean a complete stop of ET and a considerable number of the patients who chose to stop the study medication continued and completed ET outside of the trial [8].

In accordance with other studies [5, 9, 12], we found that non-compliance (11.7%) as well as non-persistence (15.6%) was highest in younger women. It was assumed that these women might not have adjusted to a diagnosis of BC as well as older women and therefore were also less willing to accept or more likely to experience therapy-related side effects [27, 28]. Furthermore, our study confirms a previous finding in postmenopausal patients that care in an oncological unit is associated with higher persistence to therapy [8]. This indicates that general practitioners might not be able to ideally lead women through conflicting situations with regards to therapy. Great demands are made on the treating physician (both on a professional and interpersonal level) in these situations and frequently, it takes several months if not years to create and maintain a sustainable therapy. These concerns must be discussed with care since greater and greater numbers of cancer patients, particularly older ones, are being treated with oral agents and considering the limitations on specialists' time, a better strategy should be developed to improve collaboration with primary care physicians [29].

Conclusions

Studies on compliance and persistence on drug intake demand a detailed follow-up of the patients and a clear description of and discrimination between different reasons of therapy cessation to clearly define the frequency of non-persistence. In order to illuminate the complex field of personal motivation to therapy, a single institution study with a more individual-based approach might better be suited to provide a detailed case documentation than the more epidemiologic approach of large database studies. Our data shows that, when compared to other studies, low non-persistence rates can be realistically achieved. Interventions are needed to support patients, particularly the younger ones, to comply with therapy. Efforts should be made to make sure that all physicians, above all general practitioners, who are involved in the treatment of BC patients, are provided with current knowledge and skills, as to guarantee an optimal patient management.

Conflict of interest The authors declare that there are no financial or personal relationships with other people or organizations that could inappropriately influence the work reported or the conclusions, implications, or opinions stated.

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