CHAPTER

9

HIGH NON-COMPLIANCE IN PATIENTS TREATED WITH EXTENDED ADJUVANT LETROZOLE. RESULTS FROM THE IDEAL RANDOMIZED TRIAL

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ABSTRACT

Background

The aim of this study was to investigate non-compliance to aromatase inhibitors and factors associated with early treatment discontinuation in the extended adjuvant setting.

Methods

The IDEAL trial is a prospective, open-label phase-III trial comparing 2.5 with 5 years of extended adjuvant letrozole in hormone receptor-positive postmenopausal early breast-cancer patients after 5 years of adjuvant endocrine therapy. The purpose of this study was to assess non-compliance in the first 2.5 years of extended adjuvant therapy. Non-compliance was defined as early discontinuation of letrozole for all reasons, excluding death or recurrence.

Results

At 2.5 years, 1215 patients were included in the analysis. Overall non-compliance probability was 18.4%, of which 85.1% discontinued due to toxicities. Analyses showed that patients with prior sequential therapy were less likely to discontinue treatment than when treated with an aromatase inhibitor (AI) or tamoxifen upfront (logrank-p=0.004). Longer treatment-free intervals also predicted more non-compliance (logrank-p=0.011). Age was not predictive of non-compliance (p=0.571). Prior surgery (mastectomy vs breast conserving surgery), both with or without radiotherapy and/or chemotherapy were also not associated with early treatment discontinuation (p=0.228 and p=0.585 respectively). Although having fewer than four positive lymph nodes predicted more non-compliance (logrank-p=0.050), age, tumor-type and locoregional treatment did not.

Conclusions

High non-compliance to extended adjuvant endocrine therapy was confirmed. Toxicities were the major reason for discontinuation, and this was not influenced by age. Longer treatment-free intervals and fewer positive lymph nodes predicted more non-compliance. Patients who underwent sequential therapy were least likely to discontinue extended adjuvant endocrine therapy.

INTRODUCTION

Aromatase inhibitors (AIs) have shown improvements in reducing both mortality and recurrence rates in postmenopausal hormone receptor-positive early breast cancer patients.[1-5] AIs are commonly prescribed as part of a sequential treatment regimen for 2-3 years after 3-2 years of tamoxifen, or as monotherapy for five years, although it has been suggested that more than five years of adjuvant treatment provides an additional benefit, even after a period of treatment discontinuation.[6] Despite prominent developments in breast cancer therapy directed at improving survival and reducing recurrence, early discontinuation of adjuvant endocrine therapy in the first five years of treatment is persistently high.[7, 8] Non-compliance rates are similar in patients treated with AIs, tamoxifen, or a sequence of both, and ranges between 40-60%. Reports confirm that these high rates are largely attributable to the presence and severity of adverse effects.[8-12]

AIs function by inhibiting the enzyme aromatase, which plays a role in converting estradiol to estrogen. Estrogen deprivation by AIs has shown profound effects on breast cancer survival and a significant reduction in recurrence rates.[13] However, inducing an early artificial menopausal status by depriving the body of circulating estrogens also gives rise to symptoms imitating menopause, including arthralgias, hot flashes, vaginal dryness, and osteoporosis.[14, 15] Steps have been undertaken to reduce the number of adverse effects that derive from the depletion of estrogens. Third-generation AIs were developed to be more selective and potently lower plasma estrogen levels through near-complete suppression of aromatase.[13, 16]

Studies show that treatment duration is directly related to clinical outcome.[17] Current standard of care is tamoxifen or an AI only or a sequence of both for the duration of five years, although evidence suggests that continuing treatment after five years may be beneficial in terms of survival.[1, 6]

Although data implies that treatment compliance is lower in patients who are older (≥85 years) or younger (<45 years), have a lower socio-economic status, experience side effects, and are prescribed therapy for longer duration, these associations are inconsistent across studies.[18, 19] These differences may, in part, result from differences in study populations, as well as variations in definitions of adherence. Patients' personal perceptions and beliefs about their illness as well as the risks, benefits and costs of their prescribed medication were found to be strong predictors of non-compliance, and have been the focus of investigations.[18-20]

To date, no other prospective clinical trial has studied non-compliance to extended adjuvant therapy in-depth. The MA.17 trial, one of the first trials to investigate more than five years of adjuvant endocrine treatment, conveyed high rates of adverse effects, but medication adherence was not reported.[21] In light of determining the optimal duration of adjuvant endocrine therapy, efficacy may be compromised when treatment is discontinued before the predetermined stop date is reached, in which case extended therapy is prescribed in vain.

This investigation discusses high rates of non-compliance found in the extended adjuvant setting in a Dutch trial on prolonged endocrine therapy, and determines which patients are at risk of early treatment discontinuation. Discerning which patients are at highest risk of non-compliance is imperative for tackling this issue effectively.

MATERIALS AND METHODS

Patient selection

The Investigation on the Duration of Extended Adjuvant Letrozole (IDEAL) trial is a prospective, randomized, open-label phase III trial evaluating the efficacy and safety of 2.5 with 5 years of adjuvant letrozole in breast cancer patients after five years of adjuvant endocrine therapy. The purpose of the present study was to assess non-compliance in the first 2.5 years of extended adjuvant therapy. Postmenopausal patients were diagnosed with hormone receptor-positive, early stage (I-IIIa) breast cancer, and adequately treated with five years of adjuvant endocrine therapy. Patients were disease-free at time of randomization. Adjuvant endocrine therapy consisted of five years of AIs only (anastrozole, exemestane or letrozole), or a sequence of 2-3 years of tamoxifen followed by 3-2 years of AIs. When AIs are contraindicated, five years of tamoxifen monotherapy is warranted. The IDEAL trial is registered with the Netherlands Trial Register (NTR3077). Appropriate approvals from local ethical committees were obtained and all patients provided written informed consent. 1262 patients from 72 hospitals were included in the present analysis and were randomized to either 2.5 or 5 years of letrozole (2.5mg once daily, orally) between April 2007 and April 2011.

Non-compliance

Non-compliance was defined as early discontinuation of letrozole before the predetermined end date for any reason, with the exception of early discontinuation due to cancer recurrence or death. Switching to a different form of endocrine therapy before the predetermined stop date was also considered non-compliance. The duration of letrozole therapy was determined by calculating the number of days between the first and last dose of letrozole during the first 2.5 years of follow-up. An intermittent break from therapy was permitted for a maximum of four weeks. Patients who died during the follow-up period and who had not reported treatment discontinuation before their death were considered compliant. Patients who never started letrozole were excluded from the analyses.

Patient and tumor characteristics

Tumor characteristics were recorded using clinical TNM classification (tumor size, regional lymph node metastases and distant metastases), estrogen receptor (ER), and progesterone receptor (PR) status. We collected data on tumor and pathological characteristics, including histological subtype, pathological grade and mitotic activity, and prior curative and locoregional therapy (type of surgery, type and duration of chemotherapy, type and duration of endocrine therapy). Patients were stratified by nodal status (node-negative or node-positive), time from last dose of prior endocrine therapy (0-<6, 6-<12, 12-27 months) and prior chemotherapy (yes/no). Treatment discontinuation was assessed during patient visits at 6 months, 1, 2 and 2.5 years after starting extended adjuvant treatment with letrozole, or in case of intermittent adverse events. Date of last follow-up, cancer recurrence or death were used as censoring, and further administrative censoring was applied at 2.5 years after randomization. The date of treatment discontinuation as well as reasons for non-compliance and (if relevant) subsequent therapy were documented prospectively.

Statistical analysis

Kaplan-Meier survival curves were used to demonstrate early discontinuation of letrozole over the follow-up period. We performed Cox regression analyses to identify factors associated with early treatment discontinuation. All analyses were performed with SPSS version 17.0 Statistical Software (SPSS Inc., Chicago Ill.).

Table 1. **Baseline characteristics of 1215 patients who started letrozole**

Characteristic	n	%	Characteristic	n	%
Age (years)			**Histological grade (BR)**		
<55	322	26.5	G1 (Well)	188	15.5
55-65	510	42	G2 (Moderate)	506	41.7
65-75	292	24	G3, G4 (Poor)	362	29.8
>75	91	7.5	unknown	159	13
ER/PR status			**Prior endocrine therapy**		
ER+ PR+	903	74.8	5 yrs tam	141	11.6
ER+ PR-	232	19.2	5 yrs AI	291	24
ER+ PR unk	29	2.4	2-3 tam → 3-2 AI	729	60
ER- PR+	39	3.2	unknown	54	4.4
ER- PR-	3	0.2	**Endocrine therapy type**		
ER unk PR+	1	0.1	Tamoxifen	141	11.6
Treatment-free period			Exemestane	185	15.2
0-<6 months	1069	88	Tam → exemestane	302	24.9
6-<12 months	64	5.3	Letrozole	31	2.6
12-27 months	82	6.7	Anastrozole	75	6.2
Tumor type			Tam → letrozole	111	9.1
Ductal	942	77.5	Tam → anastrozole	316	26
Lobular	190	15.6	unknown	54	4.4
other	83	6.8	**Prior chemotherapy**		
Tumor stage			no	401	33
pT0/pTis	4	0.4	yes	814	67
pT1 (≤2cm)	550	45.3	**Prior radiotherapy**		
pT2 (>2-≤5cm)	544	44.8	no	343	28.2
pT3 (>5cm)	72	5.9	yes	860	70.8
pT4a-c/pT4d	28	2.3	unknown	12	1
unknown	17	1.4			
Nodal status					
pN0/pN0(i+)	293	24.1			
pN1(mi)/pN1(1-3)	730	60.1			
pN2 (4-9)/pN3(≥10)	179	14.7			
unknown	13	1.1			

unk, unknown; BR, Bloom&Richardson; tam, tamoxifen; AI, aromatase inhibitor;

RESULTS

Patient and treatment characteristics

1262 patients were randomized for 2.5 or 5 years of treatment with letrozole. 1215 patients had at least one dose of letrozole during the follow-up period. 31 patients (2.6%) had a recurrence and seven patients (0.6%) died over the follow-up period. Most patients (1069, 88%) started letrozole within six months of the end of prior adjuvant endocrine therapy. Prior treatment consisted of five years tamoxifen (n=141) or an AI only (n=291), or sequential therapy of 2-3 years with an AI after 3-2 years of tamoxifen (n=729) (Table 1). Information about the number of follow-up visits was available for 1103 patients. Compliant patients visited the breast unit more frequently than non-compliant patients (median 2.07 (range 0.79-10.53) versus 2.03 visits (range 0.02-7.14), p=0.011).

The overall non-compliance probability was 18.4% within the 2.5-year follow-up period. The median follow-up time for non-compliant and compliant patients was 1.88 years (range 0.19-2.50) and 1.11 years (range 0.19-2.50) respectively, (p=0.003). Highest discontinuation rates were found in the first six months of treatment with letrozole (49.7%). A vast majority of patients (n=154, 85.1%) discontinued due to adverse events. Most commonly reported adverse events included musculoskeletal, neurological, and dermatological/skin disorders, based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Table 2). Other reasons for early discontinuation of letrozole included treatment refusal (n=18), protocol deviation (n=4), intercurrent illness (n=1) and other reasons (n=4). No difference existed between the randomized treatment groups (2.5 years vs 5 years letrozole) (logrank p=0.695). 35 patients discontinued follow-up altogether (13 non-compliant and 22 compliant patients).

Table 2. **Reasons for treatment discontinuation by adverse event***

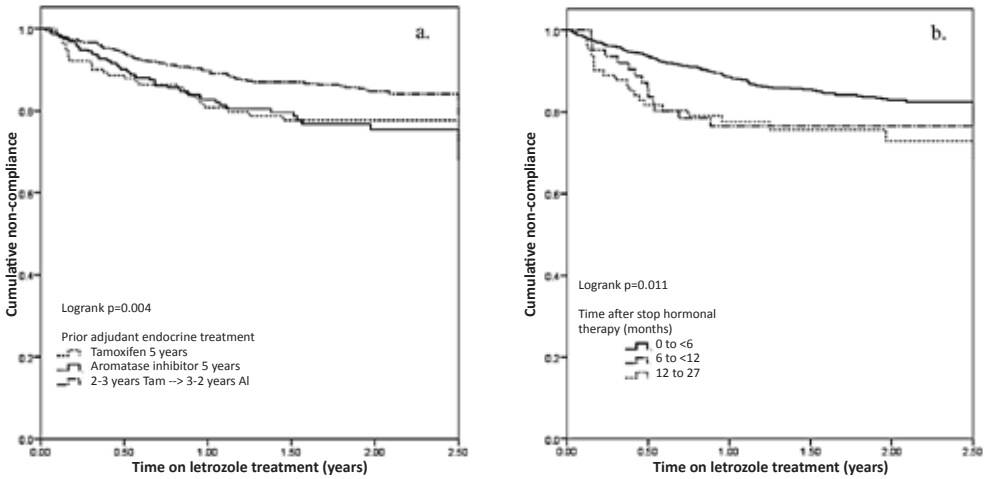
Adverse event	n	%
Cardiac symptoms	6	3.9
Constitutional symptoms	15	9.7
Dermatological / skin	17	11.0
Endocrine	7	4.5
Gastrointestinal	14	9.1
Haemorrhage / bleeding disorder	1	0.6
Infection	1	0.6
Metabolic / laboratory disorder	1	0.6
Musculoskeletal / soft tissue	29	18.8
Neurological	23	14.9
Ocular/visual	3	1.9
Pain (general)	8	5.2
Pulmonary / upper respiratory	1	0.6
Renal / genitourinary	1	0.6
Sexual / reproductive function	5	3.2
Unknown	22	14.3

* based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

Risk factors for non-compliance

A significant difference was found between treatment discontinuation and prior endocrine treatment regimen (logrank p=0.004). Patients previously treated with sequential therapy of 2-3 years tamoxifen followed by an AI for 3-2 years had the lowest probability of treatment discontinuation after 2.5 years (Figure 1a). There was no difference between the two 5-year therapies (p=0.829). Patients who had used letrozole earlier, either five years upfront or after switching from tamoxifen, were most likely to persevere

Figure 1. **Kaplan-Meier curve of early treatment discontinuation based on prior endocrine treatment regimen and treatment-free interval after 5 years of adjuvant endocrine therapy.**



a. Early treatment discontinuation based on prior endocrine treatment regimen b. Early treatment discontinuation based on treatment-free interval (months)

Figure 1a. **Early treatment discontinuation based on prior endocrine treatment regimen**

Prior treatment regimen	Non-compliance probability (%)	Discontinued treatment	(%)	HR (95% CI)	Logrank p value
Tamoxifen 2-3 → AI 3-2 years	15.6	92	12.6	1 (ref)	0.004
Aromatase inhibitor only	24.1	54	18.6	1.588 (1.056 - 2.388)	
Tamoxifen only	22.5	31	22.0	1.667 (1.191 - 2.335)	

Figure 1b. **Early treatment discontinuation based on treatment-free interval (months**

Treatment-free interval	Non-compliance probability (%)	Discontinued treatment	(%)	HR (95% CI)	Logrank p value
0 - <6	17.5	146	(13.7)	1 (ref)	0.011
6 - <12	23.4	14	(21.9)	1.702 (0.983 - 2.947)	
12 - 27	27.1	21	(25.6)	1.804 (1.140 - 2.855)	

with letrozole in the extended adjuvant setting (3.5% non-compliance, hazard ratio (HR) 0.170 (95%CI 0.066-0.437); logrank p=0.001) compared to tamoxifen only. No significant difference existed between the other treatment groups (data not shown). A significant difference was also found in the number of patients discontinuing treatment early based on the treatment-free interval between the last dose of prior endocrine therapy and the first dose of letrozole (logrank p=0.011). Longer intervals predicted more non-compliance (Figure 1b).

Patients were categorized by age (<55, 55-65, 65-75, >75 years), tumor size and nodal status based on the TNM classification, prior surgery and prior chemotherapy. No differences in early discontinuation rates between older and younger postmenopausal patients could be established (p=0.571) (data not shown). Tumor size did not show any differences in early discontinuation rates (logrank p=0.370). However, there was a barely significant difference in non-compliance based on the number of positive lymph nodes; having fewer than four positive lymph nodes predicted more non-compliance (logrank p=0.050) (Figure 2).

Figure 2. **Early discontinuation of letrozole based on nodal status**

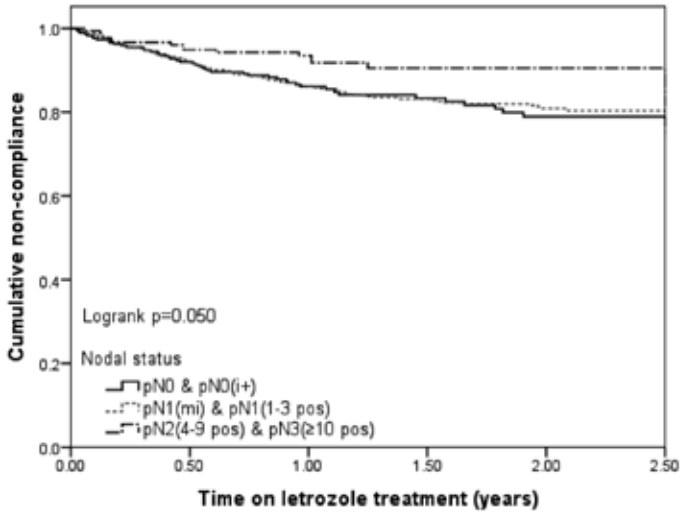


Figure 2. **Number of positive lymph nodes and treatment discontinuation**

Nodal status	Non-compliance probability (%)	Discontinued treatment	(%)	HR (95% CI)	Logrank p value
pN0 & pN0(i+)	21.1	47	16.0	1.889 (1.071 - 3.331)	0.050
pN1(mi) & pN1(1-3 pos)	19.7	117	16.0	1.874 (1.111 – 3.160)	
pN2(4-9 pos) & pN3(≥10 pos)	9.5	16	8.9	1 (ref)	

Type of surgery (mastectomy or breast conserving surgery (BCS)) was not associated with non-compliance (logrank p=0.822). Non-compliance was not associated with prior adjuvant chemotherapy (logrank p=0.585) or radiotherapy (logrank p=0.383) separately. We investigated whether the combination of surgery type with or without radiotherapy were correlated with non-compliance. Only nine patients received BCS without radiotherapy and were therefore grouped together with other breast conserving surgery patients. No differences were established between the different treatment groups (logrank p=0.228). Additional analyses were performed where patients who switched to another AI were also considered compliant. Patients with mastectomy and radiotherapy were more compliant than patients who underwent mastectomy without radiotherapy or BCS with or without radiotherapy (HR 1.740 (95%CI 1.047-2.892) and HR 1.785 (95%CI 1.113-2.864); logrank p=0.043 for the two treatment combinations respectively). After termination of letrozole, most patients discontinued extended therapy altogether (78.5%). 35 patients continued with another AI (4 patients unknown). 32 out of 35 patients switched back to the AI used prior to starting letrozole (14 exemestane, 18 anastrozole).

DISCUSSION

Risk factors for non-compliance

Non-compliance to adjuvant endocrine therapy can be detrimental for women in their treatment of hormone-receptor positive early breast cancer. More than half of the patients prescribed adjuvant AIs discontinue treatment before the five-year regimen has passed.[9, 11, 22] The present study shows that even after persisting five years of endocrine therapy, approximately 15% of patients still choose to discontinue treatment with AIs. Longer intervals between adjuvant and extended adjuvant treatment, prior endocrine therapy with tamoxifen or AI only, and fewer than four positive lymph nodes were associated with more non-compliance.

Research on non-compliance in the extended adjuvant setting after enduring five years of endocrine therapy is lacking. We found several factors that were predictive of early treatment discontinuation. The kind of endocrine therapy was an independent predictor of non-compliance. Patients previously treated with letrozole only or as part of a sequential treatment regimen were more likely to persist treatment than patients who had previously been treated with a different agent. The most plausible reasoning lies in the fact that patients are accustomed to letrozole and its toxicities.

Evidence for the impact of certain patient- and therapy-related factors on treatment non-compliance is variable. Previous reports indicate that older and younger breast cancer patients have higher rates of early treatment discontinuation.[19] Increased age is often associated with multiple comorbidities, which also affects treatment compliance.[19, 23] Non-compliance probability did not differ significantly based on age in our cohort. It should be taken into consideration that the current population may differ from other populations

reported in prior literature. Perceived benefit of extended adjuvant treatment may also be the cause of the obliterated differences in non-compliance based on age commonly described in previous studies.[18, 19] In addition, the present study population consists of patients who could be considered more compliant than the general population of postmenopausal early breast cancer patients with hormone-receptor positive disease, due to the fact that they have already completed five years of endocrine therapy.

Partridge et al. indicated that patients who underwent mastectomy instead of BCS had higher rates of tamoxifen non-compliance.[19] On the other hand, Owusu et al. reported more treatment discontinuation in patients who received BCS without radiotherapy.[22] Our results were similar to those reported by Owusu et al. only after considering patients who switched from letrozole to another AI as being compliant: patients who underwent mastectomy with radiotherapy were more compliant than those who underwent mastectomy without radiotherapy or BCS. Although mortality rates do not differ between BCS and mastectomy, a pooled analysis of randomized trials found more locoregional recurrences in patients with BCS.[24] It is therefore disquieting to discover that patients who underwent BCS with or without radiotherapy are at greater risk of non-compliance.

The observed protective effect of more positive lymph nodes on non-compliance starkly contrasts findings by Fink and colleagues.[18] Fink et al. investigated tamoxifen discontinuation in women 65 years and older with newly diagnosed hormone receptor-positive breast cancer and discovered that patients with four or more positive nodes had a two and a half times greater likelihood of discontinuing tamoxifen than patients with no positive nodes. Contrary to these findings, our study showed that patients with four or more positive lymph nodes were more compliant than patients with fewer positive nodes. This discovery suggests that patients' perceptions on the benefit of treatment and the knowledge of risk factors for disease recurrence could influence treatment persistence, as was demonstrated in earlier investigations of the role of patients' beliefs on treatment adherence.[18] All patients in our study already persisted five years of adjuvant endocrine therapy. Accordingly, patients who discontinued treatment in the first five years were not included in the present analysis. Differences between the two populations may thus explain the dissimilarity in the observations by Fink and colleagues.[18]

Adverse effects

Previous studies have recognized that non-compliance is largely attributable to the presence and severity of adverse effects.[9, 10, 19] Treatment efficacy can be compromised when AIs are not taken for the full prescribed duration.17 Adverse events were the cause of 85.1% of the cases of early treatment discontinuation, which is consistent with other studies on non-compliance in the first five years of endocrine therapy, where adverse events also posed the greatest threat to non-compliance.[9, 10, 19]

It has also been suggested that adherence to endocrine therapy is at least partially dependent on the (lack of) communication between patients and their physicians, who fail to adequately explain the importance of enduring adjuvant endocrine therapy and the potential adverse effects of the prescribed therapy.[25] As

adverse effects are a major contributor to early treatment discontinuation, it is crucial that physicians and nurse practitioners take the time to explain and prepare the patient for the possibility of adverse effects. Greater adherence was found in patients previously prescribed a sequential treatment regimen than those with upfront treatment regimens. One might infer that active reinforcement of the importance of endocrine treatment when a patient visits her physician to switch from tamoxifen to an AI provides an additional advantage to treatment adherence, because the importance of therapy is reiterated. This supposition is based on reported methods of improving adherence, which include adequately explaining and reinforcing the benefits and side effects of the prescribed medication.[25]

Several methods have been proposed to objectively measure drug compliance, including self-reports, pill counts, prescription analysis, serum or urine drug levels and microelectronic monitoring systems.[26] Although one or more of these methods is unmistakably more effective for objectively assessing compliance while on treatment, this was not possible in the current study. Given the results of the present analysis, however, it is more important to reflect whether prescribing endocrine therapy for 2.5 years or longer will be advantageous if almost 20% of patients already discontinue treatment within 2.5 years.

After discontinuing letrozole, most patients stopped treatment altogether. The decision to discontinue treatment may be a relief for patients experiencing adverse effects that interfere with daily functioning and quality of life. Conversely, other patients are more reluctant to stop treatment, given the knowledge that a growing number of studies are finding that longer treatment with AIs provide additional survival benefit. The Dutch treatment guidelines currently recommend five years of adjuvant endocrine therapy for patients with hormone receptor-positive disease. Extended adjuvant therapy is not yet standard practice, and physicians and patients may therefore decide to discontinue treatment completely rather than switch to another AI. On the other hand, almost 20% of patients who discontinued letrozole did persist with another AI, which suggests that outside of clinical trials physicians are already prescribing AIs for longer. Information on drug adherence and treatment duration after switching from letrozole to another AI were not available, and is therefore a limitation of this study. Additionally, information on why non-compliant patients had fewer follow-up visits per year was not reported. It is therefore not possible to conclude whether missing a follow-up visit was due to adverse events or due to other reasons unrelated to treatment compliance.

Treatment efficacy and drug metabolism

Although endocrine therapy is known to cause multiple toxicities of varying severity, not all patients report adverse effects. With respect to tamoxifen, patients may differ in their metabolic responses to convert tamoxifen into the active metabolite endoxifen, depending on the activity of the Cytochrome P450 2D6 (CYP2D6) enzyme.[27] Treatment efficacy seems highest in patients considered extensive metabolizers.[27-29] Goetz and colleagues found that extensive metabolizers had the highest rates of adverse effects such as hot flashes.[28] If this also holds true for AIs, it is important to determine which patients are at highest risk of non-compliance resulting from adverse events based on their metabolic characteristics. If differences in drug

efficacy are associated with variations in AI metabolism, and treatment toxicities are subsequently linked to these variations in AI metabolism, one can infer that patients with more severe adverse reactions will derive additional benefit from AI therapy. Simultaneously, these are the same patients who will have the greatest risk of non-compliance. To date, this has only been demonstrated in CYP2D6 metabolism studies with tamoxifen.[27-29] Considering that an individual-tailored approach to endocrine treatment of postmenopausal breast cancer patients is most favourable, it is crucial that future studies determine which patients are at highest risk of adverse events, and consequently, non-compliance.

Patients are frequently prescribed adjuvant therapies to further reduce the risk of relapse. However, reductions in recurrence can only be attained when patients comply with the prescribed treatment and duration. Despite promising reports of superior efficacy when endocrine treatment duration exceeds five years, many patients are plagued by adverse effects, and the risk of non-compliance raises questions on the efficacy of extended treatment in all patients. 40-60% of patients have discontinued treatment after five years of treatment [19], and an additional 18% stop in the extended adjuvant setting. This alarmingly high non-compliance reiterates the need for tackling this issue effectively. Furthermore, it is important to discern which patients are most likely to encounter adverse effects and prevent their non-compliance, as it is likely that these patients may derive most benefit from extended adjuvant endocrine therapy with AIs.

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