Uterine and quality of life changes in postmenopausal women with an asymptomatic tamoxifen-thickened endometrium randomized to continuation of tamoxifen or switching to anastrozole.

Running title: RCT comparing tamoxifen with anastrozole

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Abstract

Background: Prior to the knowledge that 5 years of adjuvant tamoxifen is less efficacious to 2-3 years tamoxifen followed by 2-3 years anastrozole/exemestane, we designed a multicenter double-blind randomized controlled trial in patients with a thickened endometrium on tamoxifen to compare uterine and quality of life parameters between those switching to anastrozole and those continuing tamoxifen.

Methods: Asymptomatic postmenopausal women, 2-3 years on adjuvant tamoxifen for operable breast cancer with a double endometrial thickness above 7mm were randomized to 20mg tamoxifen or 1mg anastrozole for the remaing duration totaling 5 years. Tablets were unrecognizable for drug assignment. The primary endpoints were the differences in double endometrial thickness and uterine volume after 1 year. Uterine and quality of life data were analyzed using regression methods and missing values handled using multiple imputation.

Results: Seventy-two patients (median age 60 years) were randomized in five hospitals. Relative to patients continuing tamoxifen, patients switching to anastrozole experienced a decrease in double endometrial thickness of 53% (95% CI 41-63%) and a decrease in uterine volume of 51% (95% CI 39-60%). Vaginal dryness (b=0.064; 95% CI 0.016 to 0.112) and sexual problems (b=0.054; 95% CI 0.007 to 0.102) increased for patients on anastrozole compared with tamoxifen. Treatment arms did not differ regarding withdrawal rate and the experience of (serious) adverse events.

Conclusion: Despite premature trial closure, our data provided valuable insights. Switching to anastrozole strongly decreased the endometrial thickness and uterine volume but increased sexual disturbances. Safe and effective interventions are needed to alleviate sexual dysfunction.

Keywords: Breast cancer, postmenopausal, endocrine treatment, endometrial thickness, uterine volume, quality of life

Introduction

Breast cancer remains the most frequent female cancer in the Western world[1]. The selective estrogen receptor modulator tamoxifen has numerous activities, one of which is blocking the estrogen receptor (ER). After cessation of a 5-year treatment, a beneficial effect remains even 10 years later. The absolute improvement in recurrence of breast cancer was greater during the first 5 years, whereas the improvement in survival grew steadily larger throughout the first 10 years. This translated in an absolute improvement in 10-year survival of 10.9% for node positive (61.4% vs 50.5% survival) and 5.6% for node negative (78.9% vs 73.3%) patients[2]. There are, however, some safety concerns relating to certain estrogenic effects of tamoxifen, including endometrial pathology like polyps and cancer[3]. Also, de novo and acquired resistance to tamoxifen prompted development of the aromatase inhibitors (AI) that inhibit the production of estrogens and lack endometrial activity with a superior efficacy over tamoxifen in the adjuvant treatment of postmenopausal ER-positive breast cancer. However, compliance with AIs is a problem because of severe menopausal symptoms like arthralgia, sexual dysfunction but also because of long term health concerns like osteoporosis, fractures and coronary heart disease. Therefore, current treatment guidelines recommend AI for 5 years only in women with a high risk for relapse whereas the switch from tamoxifen to an AI after 2-3 years or the other way around remains a viable treatment option in others. This switch strategy has a proven overall survival benefit over 5 years of tamoxifen and is not inferior to 5 years of an AI in early breast cancer[4]. AIs do not have an estrogenic effect on the uterus and may even reverse tamoxifen-associated endometrial changes[5-6].

To study the switch to anastrozole in women with a tamoxifen-primed thickened endometrium, we compared double endometrial thickness (DET), uterine volume (UV) and quality of life (QoL) between patients continuing tamoxifen and patients switching to anastrozole in a double-blind double dummy randomized controlled trial (RCT) without prior assessment or treatment of the uterine cavity.

Methods

This multi-center double-blind RCT that started in October 2004 in five Belgian hospitals enrolled non-hysterectomized postmenopausal patients who previously received tamoxifen for 2-3 years for early ER-positive breast cancer. Patients were asymptomatic with a thickened endometrium, i.e. more than 7 mm on transvaginal ultrasound (TVUS). Patients were randomized to either continuing 20mg tamoxifen (labeled TAM) or switching to 1mg anastrozole (ANA). Tablets were unrecognizable using the double dummy method. Compliance with treatment assignment was assessed by tablet count and collecting medication boxes. The objectives were to assess the effect of treatment on DET, UV, and QoL during the rest of 5 years of endocrine treatment. Block randomization was used (block length four) with stratification for center. The randomization lists were generated by an independent statistician, and were given to the pharmaceutical company where patient medication boxes were numbered. The code was revealed to the researchers once all data were collected.

The study was conducted in accordance with the Declaration of Helsinki after the protocol was approved by the Ethical Committee for Clinical Studies of the University Hospitals Leuven. All participants provided written informed consent.

All patients underwent a TVUS within 2 weeks preceding randomization (baseline), and at 1 and 2 years post-randomization unless there were symptoms of progression or vaginal bleeding. The uterus was completely assessed in sagittal and coronal planes with uterine size recorded in mm in three diameters (D_1, D_2, D_3). The volume (ml) was estimated as $(D_1*D_2*D_3*\pi)/6000$. DET was measured in the sagittal plane, from one endometrial-myometrial interface to another excluding intracavitary fluid. No interventions were performed on any asymptomatic uterine abnormalities that were detected at baseline.

At baseline, 3 months, 1 year, and 2 years, QoL was assessed through a short 8-item menopause symptom questionnaire. This questionnaire has been developed and validated at the University Hospitals Leuven[7]. The occurrence and severity of menopausal symptoms experienced for the past seven days was rated on a five-point scale ranging from 1 (not at all) to 5 (intolerable).

The primary endpoints were the differences in DET and UV between treatment arms after 1 year. Secondary endpoints were differences in DET and UV after 2 years, QoL differences, and differences in withdrawal and adverse event rates.

We planned to include 100 patients per treatment arm, as this was practically feasible and allowed for a wide margin of safety regarding power and precision. Based on available data[6], and expecting a DET increase of approximately 3 mm for TAM patients but a decrease of 3 mm for ANA patients after 1 year, power for detecting a difference would be close to 100%.

An intent-to-treat analysis was performed. Treatment effects on DET and UV after 1 and 2 years were investigated using repeated measures regression with age, baseline BMI, and baseline UV or DET as covariates. Treatment effects on QoL symptoms during the follow-up period were investigated using repeated measures proportional odds ordinal logistic regression with age, baseline BMI, and baseline symptom severity as covariates. A positive interaction effect between time and treatment arm would suggest that the symptom become more severe over time for ANA patients compared with TAM patients.

Missing values for UV, DET, and QoL symptoms were handled using multiple imputation (i.e. 20 imputations) under the *missing at random* assumption using predictive mean matching regression[10]. Rubin's rules were used to combine results from the different imputations. Imputation was done for both treatment arms separately, and was based on variables related to the occurrence of missing values, age, baseline BMI, and UV/DET/QoL measurements at other time points. A sensitivity analysis was performed by comparing the results with a complete case analysis, and with results obtained under various *missing not at random* assumptions[12].

Results

When 72 patients were randomized (37 ANA, 35 TAM) in 2008, exemestane after 2-3 years of tamoxifen became reimbursed by the Belgian health authorities following publication of the Intergroup Exemestane Study (IES)[13]. This necessitated termination of recruitment. Patients were informed of the situation, but continued with the trial and were not unblinded. The ethical committee agreed upon this.

A trial flow chart is presented in Table 1. Patient demographics and clinical characteristics of the patients at baseline did not differ between the two groups (Table 1). The median age of the patients was 60 years (interquartile range 55 to 65). Patients were on tamoxifen prior to randomization for a variable amount of time ranging from 23 to 37 months, with a median of 28 (interquartile range 24 to 33.5).

Thirty-eight patients (53%) reported adverse events, ten (14%) reported a serious adverse event, and twelve (17%) withdrew from the study. No differences between treatment arms were observed (Table 1). Arthralgia was the most frequently reported adverse event (4 ANA, 5 TAM).

Allowing a margin of 10% to account for normal measurement variation, after 1 year 91% and 93% of the ANA patients experienced a decrease in DET and UV, respectively, while 3% and 4% experienced an increase. On the contrary, 39% and 24% of the TAM patients experienced a decrease and 33% and 43% an increase. Similar results were obtained after 2 years.

DET and UV were $\log_2$-transformed in the repeated measures regression models to correct for skewness. Treatment effects at 1 year for switching to anastrozole were -1.097 for $\log_2$(DET) and -1.015 for $\log_2$(UV) (both p-values <0.0001). On average, this corresponds to a 53% (95% CI 41-63%) decrease in DET and a 51% (95% CI 39-60%) decrease in UV for patients switching to anastrozole versus patients continuing tamoxifen. Effects after two years were nearly identical. Changes in DET and UV are presented in Figure 1. The effects were similar in the complete case analysis and after multiple imputation under the assumptions that missing values were more likely if the value was high or if the value was low.

Treatment effects on menopausal symptoms were observed only for vaginal dryness and sexual problems, see Table 2. Over the two-year follow up period, these symptoms had become more severe for ANA compared with TAM patients. For instance, a patient with median age and BMI with symptom severity 1 would have a risk of increased severity (i.e., 2 or more) after two years of 51% for the ANA arm vs 18% for the TAM arm (Table 2). These results were comparable to those from the complete case analysis and those after multiple imputation under the assumption that missing values were more likely if symptom severity was high.

Discussion

In this RCT switching to anastrozole reduced DET and UV without uterine symptoms like vaginal bleeding; there was an increase in vaginal dryness and sexual problems. A significant proportion of women randomized to tamoxifen reported anastrozole-related symptoms. Our results confirm these of 9 patients switched to exemestane[6] and 17 patients switched to letrozole[5] without prior assessment or treatment of the asymptomatic tamoxifen-primed thickened endometrium. Bertelli reported this phenomenon in a substudy of IES including 183 women, all asymptomatic in the year prior to the trial[14]. At a median 55.7 month follow-up the switch to exemestane did reverse endometrial thickening with significantly fewer endometrial hyperplasia and polyps than those who continued tamoxifen[14]. We confirm this for anastrozole, such that there seems to be little need to assess the uterine cavity in an asymptomatic tamoxifen-user switching to an AI after 2-3 years. Others came to the same conclusion but first treated the uterine cavity with D&C, hysteroscopy or even hysteroscopic resections prior to starting the AI[15-19]. Some studies, including ours, reported an important decrease in DET only on the first assessment but not thereafter. In contrast, others revealed further decrement of mean DET with longer use of AIs[20-22]. It is difficult to judge to what extent these results can be explained by spontaneous endometrial thinning after discontinuation of tamoxifen in the absence of an AI[23-25]. We did not include a placebo group because this is unethical considering that 5 years of therapy is the standard. In IES[14], endometrial thinning following cessation of tamoxifen paralleled endometrial thinning following the start of exemestane. Most of the thinning effect may therefore be related to discontinuing tamoxifen rather than to the appearance of a pure anti-estrogenic effect of AI. Nevertheless, AIs are able to antagonize an estrogen-primed endometrium[26], which is effective in endometriosis[27] and considered for the management of endometrial pathologies like cancer and low grade sarcoma[28]. It remains an open question whether patients who keep a thickened endometrium following tamoxifen withdrawal remain at increased risk for endometrial cancer.

We previously observed that dyspareunia was more common on AI versus tamoxifen already after 3 months[29]. In an RCT comparing exemestane with tamoxifen, exemestane increased vaginal dryness and decreased libido after 3 and 12 months[30]. Similarly, the MA-17 trial reported poorer sexual outcomes in the letrozole group compared with the placebo group, although no specific sexual concerns like vaginal lubrication or dyspareunia were assessed[31]. The ATAC trial observed increased levels of vaginal dryness and dyspareunia, and a reduction in libido in women receiving anastrozole compared with tamoxifen[32]. However, the IES study compares best with ours. They did not find significant differences in QOL and sexual functioning when switching to exemestane after 2-3 years of tamoxifen[33]. Although few items in the questionnaires measured sexual functioning, it has previously been thought that prior adjuvant tamoxifen may neutralize the impact of AI-use on sexual dysfunction. Our results suggest that this is not the case. We stress the need for a better assessment of sexual dysfunction using psychometrically robust multidimensional instruments such as the Sexual Activity Questionnaire (SAQ) [34], among others. The SAQ has been designed to evaluate the impact of

hormonal treatment (tamoxifen) on sexual function in pre- and postmenopausal women at high risk of developing breast cancer.

Although non-hormone-containing local agents with demonstrated efficacy are available, optimal therapy for estrogen deprivation-associated vaginal/vulvar symptoms might require local or systemic estrogen use with unproven safety on breast cancer outcome, especially for women on AIs. Switching from tamoxifen to an oral AI has also been associated with a significantly higher incidence of joint pains and diarrhea. Therefore, women with non-manageable vaginal/vulvar symptoms on adjuvant AIs should consider the switch to tamoxifen rather than adding local or systemic estrogens to the AI regimen.

Conclusion

Despite premature trial closure, our data provided valuable insights. switching to anastrozole strongly decreased the endometrial thickness and uterine volume but increased sexual disturbances. Safe and effective interventions are needed to alleviate sexual dysfunction.

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Table 1. Trial flow chart, adverse event and withdrawal rates, and baseline patient characteristics.

	Treatment arm		
	Switch to Anastrozole	Continuation of Tamoxifen	Difference in percentages or medians (with 95% CI)
Randomized patients	37	35	
Baseline			
DET information	36	35	
UV information	32	29	
Complete QoL information	37	35	
3 months			
In study	*37, 100%*	*35, 100%*	
Complete QoL information	34	33	
1 year			
In study	*34, 92%*	*34, 97%*	
DET information	32	33	
UV information	29	31	
Complete QoL information	31	29	
2 years			
In study and completed	*29, 78%*	*31, 89%*	
DET information	27	31	
UV information	26	29	
Complete QoL information	27	25	
Withdrawal	8, 22%	4, 11%	11 pp (-8, 27)
Reasons for withdrawal	2x disease progression; 4x arthralgia; stomach complaints; lost to follow up	Chronic myeloid leukemia; arthralgia; hysterectomy; vaginal bleeding	
At least 1 adverse event	20, 54%	18, 51%	3 pp (-19, 24)
Serious adverse events	4, 11%	6, 17%	-6 pp (-23, 10)
	2x hip fracture; uterine prolapse (hysterectomy); curettage	Chronic myeloid leukemia; arthralgia; uterine prolapse (hysterectomy); curettage; depression; effort angor	
Months on tamoxifen, *median (range)*	30 (23-37)	28 (24-36)	2.0 months (- 3.6, 7.6)
Age (years), *median (range)*	60 (45-77)	58 (43-76)	2.4 years (-2.0, 6.8)
BMI (kg/m²), *median (range)*	25.7 (19.0-33.3)	25.6 (20.0-37.2)	0.1 kg/m² (-1.9, 2.2)
Baseline DET (mm), *median (range)*	9.4 (7-20)	11.0 (7.5-25)	-1.6 mm (-3.5, 0.2)
Baseline UV (mL), *median (range)*	52.7 (11.3-182)	59.1 (17.8-156)	-6.4 mL (-25.0, 12.3)

UV, uterine volume; DET, double endometrial thickness; QoL, quality of life; pp, percentage points

Table 2. Treatment effects on menopausal QoL symptoms using repeated measures ordinal logistic regression models with age, baseline BMI and baseline symptom severity as covariates.

Menopausal symptom	Time-by-treatment interaction, *b* (95% CI)	Summary of predictions: risk of higher symptom severity after 2 years relative to baseline for ANA vs TAM patients*	
		baseline severity 1 (not at all)	baseline severity 2 (minor inconvenience)
Hot flashes day	-0.009 (-0.054, 0.036)	26% vs 30%	16% vs 19%
Hot flashes night	0.011 (-0.037, 0.058)	24% vs 19%	19% vs 15%
Vaginal dryness	0.064 (0.016, 0.112)	51% vs 18%	37% vs 11%
Urinary problems	0.022 (-0.028, 0.071)	30% vs 20%	15% vs 9%
Emotional disturbance	-0.001 (-0.043, 0.041)	40% vs 41%	23% vs 23%
Memory problems	0.017 (-0.024, 0.057)	44% vs 35%	33% vs 25%
Joint/muscle pain	-0.005 (-0.048, 0.037)	59% vs 62%	45% vs 48%
Sexual problems	0.054 (0.007, 0.102)	38% vs 14%	27% vs 9%
Sleeping problems	0.005 (-0.035, 0.046)	42% vs 39%	42% vs 39%

* For a patient of median age and BMI (60 years and 25.7kg/m2)
Symptom severity: 1 – not at all, 2 – minor inconvenience, 3 – moderate inconvenience, 4 – severe inconvenience, 5 – intolerable

Figure 1. Evolution of double endometrial thickness (panel A) and uterine volume (panel B) by treatment arm – the predictions at 1 and 2 years are based on the regression analysis and back-transformation of the predicted log-transformed values to the original scale, the baseline values are based on the multiply imputed data sets

Summary sentences for table of contents

In postmenopausal asymptomatic breast cancer patients with a tamoxifen-thickened endometrium, switching to anastrozole after 2-3 years on tamoxifen strongly decreased the endometrial thickness and uterine volume but increased sexual disturbances.

Figure

