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CLINICAL TRIAL

# A phase III randomized multicenter trial evaluating cognition in post-menopausal breast cancer patients receiving adjuvant hormonotherapy

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**Abstract** Cognitive impairment, especially verbal episodic memory and executive function impairments, has been considered to be a possible adverse effect of aromatase inhibitors (AI). This phase III open-label study compared the impact of tamoxifen and AI on verbal episodic memory (Rey auditory verbal learning test—RAVLT) and other cognitive functions (visual memory, psychomotor speed, and executive functions) after 6 and 12 months of treatment in breast cancer patients undergoing adjuvant hormonotherapy. Menopausal chemo-naïve patients with resectable breast cancer were randomly assigned (1:1) at the end of the radiotherapy to receive tamoxifen or AI. Neuropsychological assessments, self-reported quality of life, and depression assessments were performed at baseline, before any hormonal treatment, and at 6 and 12 months. Mixed design analysis models of variance was used to compare the evolution of the scores between the groups during follow-up. A total of 74 evaluable patients were enrolled (Tamoxifen arm, $n = 37$; AI arm, $n = 37$; letrozole $n = 18$; anastrozole $n = 16$; exemestane $n = 3$). The median age at inclusion was 61 years (range, minimum 49–maximum 69). The patient and breast cancer characteristics were well balanced between arms. After 6 months, no significant differential effect of AI or tamoxifen was observed on the RAVLT. Moreover, considering the other cognitive measures and the quality of life questionnaires, there were also no differences between the groups during the 1-year follow-up. In this study, AI has not demonstrated worse adverse effects on cognitive functions than tamoxifen during a 1-year follow-up

**Keywords** Cognitive disorders · Breast cancer · Hormonotherapy · Aromatase inhibitors · Tamoxifen · Chemobrain

## Introduction

Approximately, 60 % of breast cancers (BC) express estrogen receptors [1]. Hormonotherapy is thus widely used in the adjuvant treatment of hormone-sensitive BC. Tamoxifen, a selective estrogen receptor modulator, alters hormone action by binding to estrogen receptors. Tamoxifen is recognized as having a mixed estrogen agonist/antagonist effect, but its action on the brain is still under

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debate. Aromatase inhibitors (AI) decrease the in situ conversion of androgen to estrogens and induce a lower concentration of plasma estrogen than tamoxifen in early-stage BC [2].

Estrogen and AI receptors have been identified in several areas of the brain involved in cognition, especially the hippocampus and related cortical areas [3–5]. Thus, hormonotherapy could influence cognitive disorders that may induce a negative impact on quality of life and reduce adherence to treatment [6]. In most of the studies on BC, a negative impact of hormonotherapy was reported, especially on verbal memory and executive functions [7, 8]. A more profound effect of AI on cognition than Tamoxifen has been discussed, due to a more important reduction of estrogen concentration in the plasma [9]. Nevertheless, numerous methodological limits have been observed in these studies and only a few have been performed on a dedicated chemo-naïve early BC population.

The primary objective of our study was to evaluate the verbal episodic memory according to the scores in the Rey auditory verbal learning test (RAVLT) after 6 months of treatment (AI or tamoxifen) in post-menopausal and chemo-naïve BC patients. The secondary objectives were the evaluation of other cognitive functions (memory, psychomotor speed, and executive functions) at 6 months of treatment, the evaluation of the whole cognitive tests at 12 months, and the evaluation of quality of life at 6 and 12 months.

## Methods

### Eligibility criteria

Inclusion criteria included the following: newly diagnosed histologically confirmed BC, the expression of estrogen or progesterone receptors (ER, PR) defined by a rate >10 % of hormonal receptors expression in the tumor determined by immunohistochemistry tests, indication of adjuvant hormonotherapy (T0–T2 tumors without nodal metastases, expressing ER or PR but without HER2 positivity), post-menopausal status defined by amenorrhea persisting for an entire year or oophorectomy confirmed by the FSH and 17beta-estradiol levels, and French native speakers with a Karnofsky performance status (KPS) ≥80. Exclusion criteria included the following: a history of personal or familial thrombo-embolic disease, metastatic disease, previous chemotherapy, being ≥70 years of age to reduce the rate of concomitant undiagnosed neurological degenerative pathology, a history of depression or other psychiatric disease, and undergoing psychotropic treatment (neuroleptics and long-life benzodiazepines) or using anticholinesterase agents.

All patients signed a consent form approved by the local ethics committee (North West ethics committee of France) on September 9th, 2008. The study was identified on Clinical Trials.gov as NCT00893061.

### Study design and treatment plan

This phase III multicenter open-label study randomly assigned patients 1:1 per block of 6, without stratification factors, to receive oral tamoxifen (20 mg/day) or oral AI (letrozole 2.5 mg/day, anastrozole 1 mg/day, and exemestane 25 mg/day at the discretion of the referring oncologist). All three of these AIs are supposed to induce the same level of estrogen depletion due to a class effect and were thus authorized. The initial hormonotherapy could be changed after 1 year of treatment at the end of the study. Hormonotherapy was continued until disease recurrence or unacceptable toxicity during the 1-year study period. The standard follow-up of BC was not changed.

### Assessments

Detailed neuropsychological assessments, questionnaires on autonomy in daily living (instrumental activity daily living—IADL scale), quality of life-C30 (QLQ-C30), and emotional state [hospital anxiety and depression scale (HADS)] were performed before the first administration of hormonotherapy and then after 6 and 12 months of hormonotherapy.

### Cognitive assessments

Trained neuropsychologists, blinded to the treatment group, administered the standard neuropsychological testing. The hand dominance (Edinburgh Handedness Inventory [10]) and a premorbid intellectual functioning test (French adaptation of the National Adult Reading Test, fNART [11]) were assessed at the time of inclusion. A specific cognitive battery was then administered at baseline, 6, and 12 months of treatment. This battery consisted of a questionnaire on self-report cognitive functioning complaint (cognitive difficulties scale (CDS) [12]), a test of global cognitive functioning (mini mental state examination (MMSE) [13]), and specific tests for the assessment of episodic memory, working memory, processing speed, and executive function. Verbal episodic memory was evaluated with the Rey auditory verbal learning test (RAVLT) [14] (sum of words learned across trials 1–5, used as primary endpoint, immediate (trial 6 recall) and delayed (trial 7) free recall used as secondary endpoints), while the Benton Visual Retention Test (BVRT [15], multiple-choice administration) was proposed for the evaluation of visual episodic memory (number of correct answers). Working

memory was assessed with the forward and backward digit span [16] (number of correct sequences) for the verbal part and the visuo-spatial component with the spatial subtest of the Wechsler Memory Scale [17] (number of correct sequences). Psychomotor speed was assessed using completion time (in seconds) for part A of the trail making test [18] and the color naming part of the Stroop test [19]. Executive functions were evaluated by the letter and category fluency tasks [20] (number of words generated), the trail making test (Trails B/Trails A ratio), the Stroop test (interference ratio), and the Wisconsin card sorting [21] test (number of perseverative errors). All the neurocognitive tests used in this trial are sensitive, reliable, reproducible, and have normative data. Parallel forms were used for the episodic memory tests (RAVLT and BVRT) to limit test–retest effects. The duration of the neuropsychological testing was approximately 1 h and a half. The neuropsychological testing is reported in Table 1.

### Quality of life, autonomy in daily life and emotional assessments

Quality of life was assessed according to the QLQ C-30 self-administered questionnaire [22], which is composed of five functional scales, nine symptoms scales, and a two-item global quality of life scale (QoL). Autonomy in daily life was evaluated with a 4-item self-administered instrumental activity of daily living (IADL) questionnaire [23]. The emotional state was determined by the self-administered HADS. Only adverse events of grade 3–4 were prospectively reported in this study according to the CTCAE v.4.

### Statistical methods

The main objective of this trial was to compare the changes observed in episodic verbal memory between baseline and 6 months of hormonotherapy in each arm (patients receiving tamoxifen vs. AI). The RAVLT score, sum of words learned across trials 1–5, was chosen as the primary endpoint. The estimated mean (±SD) for this score is 49 (±8) in the 50–70-year-old population. A cognitive decline is diagnosed in the case of a variation of one standard deviation (eight points). Considering a two-sided independent $t$ test (with type I error rate of 5 and 95 % power), and an expected difference of eight points, 27 evaluable patients per arm were needed for the analysis at 6 months. Taking into account potential drop-outs, 74 patients (37 per am) were sought for enrollment. Analyses were performed in the intent to treat population.

Descriptive statistics were used for the characterization of the patient sample. Comparisons between the two groups of patients (tamoxifen vs. AI) at baseline were performed using the two-sample $t$ test or the Wilcoxon rank-sum test as a non-parametric alternative when the assumption of normality was not respected.

Analysis of covariance (ANCOVA) adjusted for baseline performance was then used to compare the performance at 6 months of the RAVLT score between the groups (tamoxifen vs. AI).

**Table 1** Summary of the cognitive test measures and outcome variables

| Cognitive domain | Cognitive tests | Outcome variable | Score range |
|---|---|---|---|
| Cognitive complaint | Cognitive difficulties scale (CDS) | Total score | 0–159 |
| Global cognitive functioning | MMSE | Total score | 0–30 |
| Verbal episodic memory | Rey auditory verbal learning test (RAVLT) | Sum of words learned across trials 1–5 | 0–15 |
| | | Immediate free recall | 0–15 |
| | | Delayed free recall | 0–15 |
| Visual episodic memory | Benton visual retention test (BVRT) | Total score | 0–15 |
| Working memory | Forward digit span | Number of correct sequences | 0–14 |
| | Backward digit span | | 0–14 |
| | Forward spatial span | | 0–14 |
| Psychomotor speed | Part A of the trail making tests | Completion time in seconds | 0+ |
| | Naming part of the Stroop task | | 0+ |
| Executive functions | Letter fluency | Number of correct words | 0+ |
| | Category (animal) fluency | Number of correct words | 0+ |
| | Trail making test | Trails B/Trail A ratio | |
| | Stroop test | Interference ratio | |
| | Wisconsin card sorting test | Number of perseverative errors | 0–47 |

Secondary objectives were analyzed with mixed model analyses of variance (adjusted for baseline performance) to compare the evolution of the cognitive scores between the groups during follow-up, with groups (tamoxifen vs. AI) as the between-subjects variable and time (6 and 12 months testing) as the within-subjects variable. Adjusted mean (±SE) was calculated when there was a significant effect (group, time, or interaction). Moreover, scores from the cognitive battery for each individual and at each visit (baseline, 6, and 12 months visits) were compared to normative data and were classified as within the normal range or pathological (when the score was 1.65 standard deviation below the mean from available normative data).

Mixed model analyses adjusted for baseline were also used for emotional state (HADRS) and biological data. Concerning the quality of life questionnaire, Fisher's exact test were used to compare proportion of patients from each group showing a decrease in the global and functional scale scores from the QLQ C-30 between baseline and 6 months visit (subtracting the score at baseline from the 6 months visit) as well as between baseline and 12 months visit (subtracting the score at baseline from the 12 months visit). The same procedure was used for the symptom scale but we considered here the increase of the score on these scales between baseline and 6 months visit as well as between baseline and 12 months visit. The same procedure was considered for the autonomy score.

Analyses were performed on SAS software version 9.3 (SAS Institute, Cary, NC, USA).

## Results

### Patient characteristics

A total of 74 women were prospectively enrolled in three French centers from March 2009 to April 2011. Consecutively, deemed eligible patients were randomly assigned: 37 in the tamoxifen arm and 37 in the AI arm. At baseline, the patient characteristics were well balanced between the two arms (Table 2). Specifically, no difference was observed for age, handedness, premorbid intellectual functioning, BC characteristics, body mass index, and the 17beta-estradiol or FSH levels. Patients in the tamoxifen arm tended to report less cognitive difficulties than patients in the AI arm ($16.97 \pm 8.36$ vs. $20.58 \pm 9.3$, $p = 0.09$). Note, however, that no patient had at baseline a significant complaint compared to normative data.

On study compliance for the neuropsychological testing is detailed in the CONSORT diagram (Fig. 1) and in Table 3 for each test. At baseline, no significant differences were observed between the groups for the different cognitive scores (Table 4) or the different questionnaires (QLQ C-30, IADL and HADS). At the individual level, all the patients performed within the normal range for the different scores of the RAVLT. However, other measures of cognitive functioning were more frequently impaired in our BC population at baseline than expected according to available norms (which usually considered a 5 % misclassification error rate): 24 out of 70 (34 %) showed a pathological Trails B/Trails A ratio and 20 out of 70 (29 %) showed pathological scores on the verbal working memory span tasks. Proportion of pathological score for the other cognitive scores did not differ from a 5 % error rate.

### Efficacy

ANCOVA analysis of the RAVLT score (sum of words learned across trials 1–5) adjusted for baseline performance did not detect any significant change between the tamoxifen and AI arms ($p = 0.15$). Mixed model analyses used to analyze the secondary cognitive endpoints, did not show any effect on measures of episodic memory, processing speed, or executive functions between groups or time (6 and 12 months visit). There was moreover no specific effect for verbal working memory scores, but there was a group effect for the visual working memory test with AI patients showing better score than tamoxifen patients at the 6 and 12 months visits when performance was adjusted for baseline scores (Table 5). At the individual level, there was, however, only one patient (receiving AI) with a pathological score for the visual working memory test at baseline, two at the 6 months visit (one receiving AI and the other tamoxifen), and one at the 12 months visit (receiving tamoxifen). Note also that there was no group effect for the CDS but there was a significant time main effect ($p = 0.049$) showing that cognitive complaint increased between the 6 months ($19.15 \pm 0.81$) and the 12 months ($20.74 \pm 0.84$) visits (one patient had a significant cognitive complaint compared to normative data at the 12 months visit). Furthermore, proportion of pathological scores did not increase in the population between the visits for the different cognitive scores (trail making test and verbal working memory scores were more frequently impaired for breast cancer patients compared to normative data without any increase in prevalence between the different visits).

For the emotional state, mixed model analyses were also conducted and we did not observe any significant effect for the depression score as well as for the anxiety score of the HADS. Note also that we ran all previous analysis on cognitive scores with the HADS depression score as a covariate and results were unchanged (Table 5). Quality of life was then analyzed considering the proportion of patients in each group showing between the visits and

**Table 2** Demographic and histological characteristics of the patients at inclusion

| | Whole population | Arm A (tamoxifen) | Arm B (AI) | *p* |
|---|---|---|---|---|
| Median age at inclusion (years) | 61.0 (49–69) | 62.0 (53–69) | 61.0 (49–69) | 0.24 |
| Edinburgh laterality score | 58.5 (16–60) | 57.5 (16–60) | 60 (25–60) | 0.18 |
| Premorbid intellectual functioning (NART scale) | 28.5 (11–40) | 30 (12–40) | 27.5 (11–39) | 0.26 |
| Body mass index | | | | 0.52 |
| Normal | 26 (40 %) | 10 (33 %) | 16 (46 %) | |
| Overweight | 23 (35 %) | 11 (37 %) | 12 (34 %) | |
| Obesity | 16 (25 %) | 9 (30 %) | 7 (20 %) | |
| ECOG-performance status score | | | | 0.52 |
| 0 | 63 (89 %) | 32 (91 %) | 31 (86 %) | |
| 1 | 8 (11 %) | 3 (9 %) | 5 (14 %) | |
| Median FSH level (UI//) | 71 (6–110) | 75 (40–107) | 68 (6–110) | 0.46 |
| Median 17β oestradiol level (μmol/L) | 35 (10–115) | 36 (15–82) | 35 (10–115) | 0.41 |
| Surgery | | | | |
| Total mastectomy | 12 (16 %) | 3 (8 %) | 9 (24 %) | 0.08 |
| Partial mastectomy | 61 (82 %) | 33 (89 %) | 28 (76 %) | |
| Zonectomy | 1 (1.5 %) | 0 (0 %) | 1 (3 %) | |
| Radiotherapy | 63 (87.5 %) | 31 (86 %) | 32 (89 %) | 0.72 |
| Tumor (T) | | | | 0.71 |
| T0 | 1 (1.5 %) | 0 (0 %) | 1 (2.5 %) | |
| T1 | 66 (90 %) | 34 (92 %) | 32 (86.5 %) | |
| T2 | 7 (9.5 %) | 3 (8 %) | 4 (11 %) | |
| Nodes (N) | | | | 1.00 |
| N0 | 70 (94.5 %) | 35 (94.5 %) | 70 (94.5 %) | |
| N1 | 4 (5.5 %) | 2 (5.5 %) | 4 (5.5 %) | |
| Metastases (M) | | | | |
| M0 | 100 % | 100 % | 100 % | – |
| Histology | | | | |
| Invasive ductal carcinoma | 61 (82.5 %) | 30 (81 %) | 31 (84 %) | 1.00 |
| Invasive lobular carcinoma | 8 (11 %) | 4 (11 %) | 4 (11 %) | |
| Other | 5 (7 %) | 3 (8 %) | 2 (5 %) | |
| SBR grade | | | | 0.15 |
| I | 35 (47 %) | 15 (40.5 %) | 20 (54 %) | |
| II | 37 (50 %) | 22 (59.5 %) | 15 (40.5 %) | |
| III | 2 (3 %) | 0 (0 %) | 2 (3 %) | |
| ER positivity | 74 (100 %) | 74 (100 %) | 74 (100 %) | – |
| PR positivity | 59 (80 %) | 28 (76 %) | 31 (84 %) | 0.70 |
| HER2 positivity | 0 (0 %) | 0 (0 %) | 0 (0 %) | – |

*N* (%) is provided for categorical variables and the median (minimum–maximum) is provided for continuous variables

*BC* breast cancer, *ECOG* Eastern Cooperative Oncology Group, *AI* aromatase inhibitors, *FSH* follicle stimulating hormone, *SBR* Scarf Bloom Richardson, *ER* estrogen receptors, *PR* progesterone receptors, *HER 2* human epidermal growth factor receptor

baseline a decrease of their score on the functional scale and global scale or an increase on the symptom scales (Table 6). Using Fisher's exact test, only one statistical tendency was observed between the baseline and 6 months visit for the role functional scale ($p = 0.05$; more patient in the AI group than the tamoxifen group assigned a lower score for this functional scale at the 6 months visit compared to baseline). There was, however, no differential change between the groups for the different QLQ C-30 scales between the baseline and 12 months visits. Finally, we did not analyze the autonomy questionnaire as there was no observation of decreased autonomy on this scale at

**Fig. 1** CONSORT diagram

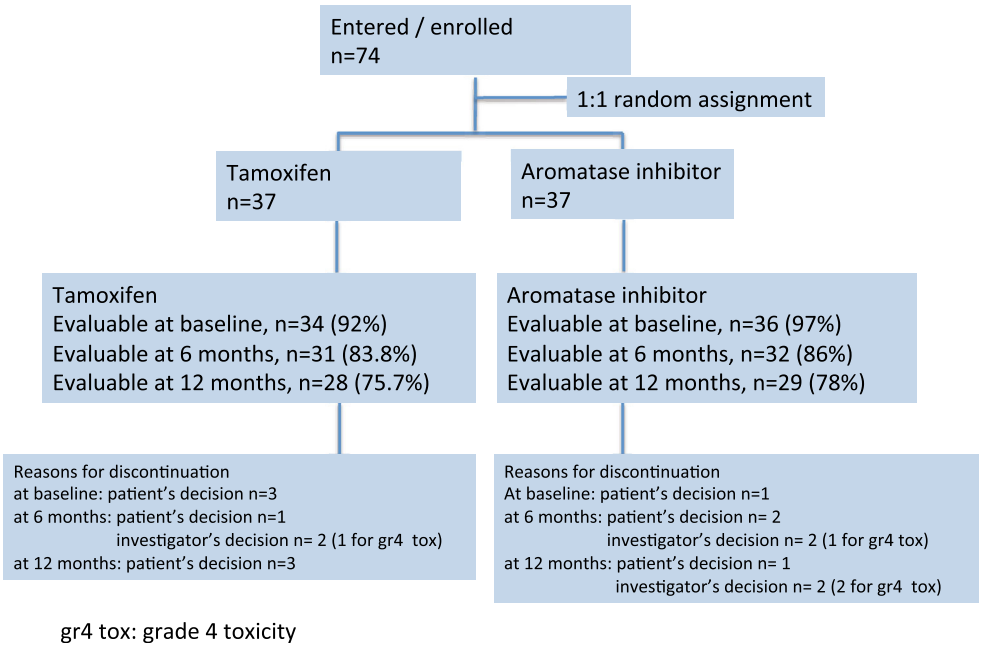


**Table 3** Longitudinal follow-up of the cognitive scores, HADS score, and quality of life scores: rates of completion of the scales

| | TAM (37 patients enrolled) | | | IA (37 patients enrolled) | | |
|---|---|---|---|---|---|---|
| | Baseline ($n = 34$) | M6 ($n = 31$) | M12 ($n = 28$) | Baseline ($n = 36$) | M6 ($n = 32$) | M12 ($n = 29$) |
| Verbal episodic memory (RAVLT) | | | | | | |
| Sum of words learned across trials 1–5 | 34 | 31 | 26 | 36 | 32 | 29 |
| Immediate free recall | 34 | 30 | 26 | 36 | 32 | 31 |
| Delayed free recall | 34 | 31 | 26 | 36 | 32 | 29 |
| Cognitive difficulties scale | 34 | 31 | 26 | 36 | 32 | 31 |
| MMSE | 34 | 31 | 26 | 36 | 32 | 31 |
| Benton visual retention test | 34 | 31 | 26 | 36 | 32 | 29 |
| Working memory | | | | | | |
| Forward digit span | 34 | 31 | 25 | 36 | 31 | 29 |
| Backward digit span | 34 | 31 | 25 | 36 | 31 | 29 |
| Forward spatial span | 34 | 31 | 25 | 36 | 31 | 29 |
| Psychomotor speed | | | | | | |
| Time completion part A trail making tests | 34 | 31 | 26 | 36 | 32 | 31 |
| Time completion naming part Stroop task | 34 | 31 | 26 | 35 | 31 | 30 |
| Executive functions | | | | | | |
| Letter fluency | 34 | 31 | 26 | 36 | 32 | 29 |
| Category (animal) fluency | 34 | 31 | 26 | 36 | 32 | 29 |
| Trail making test | 34 | 31 | 26 | 36 | 32 | 31 |
| Stroop test | 34 | 31 | 26 | 35 | 31 | 30 |
| Wisconsin card sorting test | 33 | 31 | 25 | 31 | 32 | 29 |
| HADS global score and subscores | 34 | 31 | 26 | 35 | 31 | 29 |
| QLQ-C30 score | 33 | 18 | 21 | 29 | 24 | 22 |

*n* number of patients who completed the tests

**Table 4** Cognitive scores at inclusion

| | TAM ($n = 37$) | IA ($n = 37$) | $p$ value* |
|---|---|---|---|
| Verbal episodic memory (RAVLT) | | | |
| Sum of words learned across trials 1–5 | 50.76 (8.86) | 49.58 (10.12) | 0.61 |
| Immediate free recall | 10.38 (2.45) | 10 (2.75) | 0.54 |
| Delayed free recall | 10.44 (2.71) | 10.42 (3.23) | 0.97 |
| Cognitive difficulties scale | 16.97 (8.36) | 20.58 (9.30) | 0.09 |
| MMSE | 29 [27, 29] | 29 [27.5; 29.5] | 0.57 |
| Benton visual retention test | 13 [11, 14] | 12.5 [11, 14] | 0.34 |
| Working memory | | | |
| Forward digit span | 6 [5, 7] | 6 [5, 7] | 0.69 |
| Backward digit span | 5 [4, 7] | 5 [4, 6] | 0.83 |
| Forward spatial span | 8 [7, 9] | 7.5 [6; 8.5] | 0.12 |
| Psychomotor speed | | | |
| Time completion for part A of the trail making tests | 35.5 [31, 45] | 35 [28.5; 42] | 0.36 |
| Time completion for the naming part of the Stroop task | 63 [57; 69] | 66 [59; 73] | 0.38 |
| Executive functions | | | |
| Letter fluency | 20.26 (6.44) | 19.86 (7.62) | 0.81 |
| Category (animal) fluency | 27.32 (8.57) | 28.92 (10.26) | 0.48 |
| Trail making test | 2.45 [2.1; 2.9] | 2.79 [1.9; 3.6] | 0.34 |
| Stroop test | 0.28 [0.2; 0.4] | 0.29 [0.2; 0.4] | 0.67 |
| Wisconsin card sorting test | 3 [1, 5] | 2 [0; 6] | 0.56 |

Data are mean (SD) or median [interquartile range]

*TAM* tamoxifen, *AI* aromatase inhibitors

* $t$ test or Wilcoxon rank-sum test

either the 6 or 12 months visits (each patient score 4 on this scale which reflect a preserved autonomy for the four activities considered in the questionnaire).

### Biological data

A significant modification of the FSH levels was observed during follow-up between the groups ($p < 0.001$), with a decrease in the values for the tamoxifen group (mean FSH levels at baseline = 72.7 UI/L ± 18.4; 6-month visit = 48.2 UI/L ± 16.9; and 12-month visit = 43.0 UI/L ± 14.8), while they remained stable in the AI group (baseline = 68.4 UI/L ± 22.1; 6-month visit = 78.4 UI/L ± 21.5; and 12-month visit = 69.5 UI/L ± 25.9). The levels of 17beta-estradiol were stable during follow-up in both groups. The levels of 17beta-estradiol were stable during follow-up in both groups. A decrease in the levels of 17beta-estradiol is expected with IA but only a non-significant decrease ($p = 0.08$) was observed in our study when we contrast the value at baseline against the 12-month visit values (mean 17beta-estradiol in the AI group at baseline = 35.8 pmol/l ± 24, at 6 months 27.5 pmol/l ± 28.5, at 12 months 22.6 pmol/l ± 12.2), which might be explained by the small number of patients who underwent biological analyses during the study ($n = 25$ at inclusion, $n = 17$ at 6 months and $n = 14$ at 12 months).

### Safety

A total of five patients discontinued hormonotherapy because of adverse events during the study (CONSORT diagram). A tamoxifen-related grade 4 pulmonary embolism was reported. In the AI arm, three grade 4 adverse events were observed: seizure, non-related to treatment; AI hot flashes; and AI-related arthralgia.

## Discussion

In our multicenter prospective randomized trial, no specific differential effect was found between the tamoxifen and AI arms in the cognitive, emotional, and quality of life measures in post-menopausal early BC patients after 6 and 12 months of treatment. The cognitive impact of endocrine therapies in BC patients has been evaluated in several studies with discordant findings. These conflicting results may be explained by several methodological inconsistencies such as populations with or without previous chemotherapy, the inclusion of pre- or post-menopausal

**Table 5** Longitudinal follow-up of the cognitive scores and emotional scores

| | TAM | | | IA | | | *p* value* |
|---|---|---|---|---|---|---|---|
| | M0 | M6 | M12 | M0 | M6 | M12 | |
| Verbal episodic memory (RAVLT) | | | | | | | |
| Sum of words learned across trials 1–5 | 50.8 (8.9) | 46.7 (10.6) | 47.6 (9.8) | 49.58 (10.1) | 49 (12) | 49.7 (9.7) | 0.91 |
| Immediate free recall | 10.4 (2.5) | 10 (3.6) | 9.2 (3.5) | 10 (2.8) | 10.3 (3.6) | 9.9 (3.7) | 0.47 |
| Delayed free recall | 10.4 (2.7) | 10.3 (2.9) | 9.7 (2.9) | 10.4 (3.2) | 10.2 (3.7) | 10.2 (3.8) | 0.39 |
| Cognitive complaint | | | | | | | |
| Cognitive difficulties scale | 16.9 (8.3) | 16.3 (8.7) | 19.1 (9.7) | 20.6 (9.3) | 21.8 (10.2) | 22.5 (11.5) | 0.45 |
| Global cognitive functioning | | | | | | | |
| MMSE | 28.2 (1.6) | 28.2 (1.8) | 28.5 (1.5) | 28.3 (1.7) | 28.3 (2) | 28.2 (1.9) | 0.78 |
| Visual episodic memory | | | | | | | |
| Benton visual retention test | 12.6 (1.8) | 12.9 (1.5) | 13.2 (1.2) | 12.1 (1.8) | 13.2 (1.9) | 12.8 (1.1) | 0.12 |
| Working memory | | | | | | | |
| Forward digit span | 6.1 (1.7) | 6.4 (2.1) | 6.8 (2.3) | 6.3 (1.9) | 6.6 (1.9) | 6.7 (2.2) | 0.61 |
| Backward digit span | 5.4 (2.2) | 5.7 (2.5) | 6.3 (2.5) | 5.5 (2.1) | 5.6 (2.4) | 5.8 (2.1) | 0.65 |
| Forward spatial span | 8.2 (1.5) | 7.7 (1.7) | 7.8 (1.5) | 7.7 (1.9) | 8 (1.7) | 7.8 (1.7) | 0.6 |
| Psychomotor speed | | | | | | | |
| Time completion part A trail making tests | 38.3 (10.7) | 34.2 (9.5) | 32.7 (7.6) | 35.7 (11.4) | 35.3 (13.5) | 34.1 (11.2) | 0.52 |
| Time completion naming part Stroop task | 65 (12.9) | 65.2 (11.5) | 62 (8.5) | 68.6 (20.6) | 64.6 (12.6) | 63.6 (12.6) | 0.64 |
| Executive functions | | | | | | | |
| Letter fluency | 20.2 (6.4) | 21.1 (7.1) | 22.3 (6.2) | 19.8 (7.6) | 21.3 (8.2) | 21.5 (8.1) | 0.76 |
| Category (animal) fluency | 27.3 (8.6) | 28.8 (7.1) | 28.9 (8.1) | 28.9 (10.2) | 30.2 (12) | 29.1 (10.6) | 0.70 |
| Trail making test | 2.9 (1.8) | 3.2 (2) | 3.1 (2) | 3.4 (2.4) | 2.9 (2.5) | 2.7 (1.9) | 0.56 |
| Stroop test | 0.29 (0.1) | 0.28 (0.1) | 0.28 (0.08) | 0.29 (0.13) | 0.29 (0.08) | 0.28 (0.1) | 0.22 |
| Wisconsin card sorting test | 14.5 (4.2) | 15.6 (4.6) | 16.9 (3.7) | 15.5 (4.4) | 16.4 (3.3) | 17 (3.1) | 0.27 |
| Emotional state | | | | | | | |
| HADS global score | 12.2 (6) | 11.1 (6.2) | 10.3 (5.6) | 12.3 (6.5) | 11.4 (5.5) | 12.7 (6) | 0.22 |
| Anxiety | 8.6 (3.8) | 7.3 (3.5) | 7.4 (3.7) | 8.7 (4.1) | 8.2 (3.8) | 8.6 (3.6) | 0.96 |
| Depression | 3.5 (3) | 3.7 (3.4) | 3.1 (2.6) | 3.5 (2.9) | 3.2 (2.2) | 3.9 (2.9) | 0.12 |

Data are mean (standard deviation)

*TAM* tamoxifen, *AI* aromatase inhibitors

* Mixed model adjusted for baseline performance (group × time interaction)

women, differences in assessment tools (self-reported assessment and standardized neuropsychological testing), the existence of a baseline treatment, the timing of follow-up, differences in the evaluation of adherence rates, dedicated studies or sub-studies or cohorts, the sample size, and the co-evaluation of anxiety and depression [9, 24–26]. Moreover, only a few studies or cohorts have already evaluated the effect of hormonotherapy alone on cognition in chemo-naïve patients.

The RAVLT, an episodic verbal memory test, requires the integrity of the hippocampal area, which is rich in estrogens, and was thus chosen as main criteria of evaluation. Indeed, in the previous studies, no specific test was chosen as primary endpoint but when a significant cognitive impact of hormonotherapy was observed, verbal memory and executive functions were mostly impaired [8, 9, 27–29]. RAVLT has been also selected by other authors to evaluate the verbal memory [8, 9]. The main goal was to determine the neuropsychological impact after 6 months of treatment and patients were follow-up during 1 year. In the previous studies, patients were evaluated at different times during the follow-up (range: minimum at least 3 months of hormonotherapy—maximum 36 months [9, 27, 28].

Data on the cognitive impact of anastrozole and tamoxifen are not consistent in the literature. In different studies, a detrimental effect of tamoxifen or anastrozole was observed in verbal memory and processing speed in post-menopausal chemo-naïve patients compared to controls [26–29]. In another study, a significant detrimental effect on speed measures of letter fluency, complex visuo-

**Table 6** Longitudinal follow-up of the quality of life

| | TAM | | | IA | | |
|---|---|---|---|---|---|---|
| | M0 | M6 | M12 | M0 | M6 | M12 |
| QLQ-C30 | | | | | | |
| Functional scales | | | | | | |
| Physical | 86 [80, 93] | 93 [80, 100] | 86 [86, 100] | 93 [80, 100] | 90 [83, 93] | 93 [80, 93] |
| Role | 100 [83, 100] | 100 [100, 100] | 100 [100, 100] | 100 [83, 100] | 91 [66, 100] | 100 [100, 100] |
| Cognitive | 100 [83, 100] | 100 [83, 100] | 83 [83, 100] | 100 [83, 100] | 100 [66, 100] | 83 [83, 100] |
| Emotional | 83 [66, 100] | 83 [66, 100] | 75 [66, 100] | 90 [66, 100] | 80 [70, 100] | 70 [66, 100] |
| Social | 100 [83, 100] | 100 [100, 100] | 100 [100, 100] | 100 [100, 100] | 100 [75, 100] | 100 [83, 100] |
| Symptoms scales | | | | | | |
| Fatigue | 0 [22, 33] | 22 [11, 33] | 22 [0, 33] | 16 [0, 22] | 19 [5, 33] | 22 [0, 33] |
| Nausea | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] |
| Pain | 0 [0, 33] | 16 [0, 33] | 0 [0, 16] | 0 [0, 16] | 33 [0, 41] | 8.3 [0, 50] |
| Dyspnea | 0 [0, 33] | 0 [0, 0] | 0 [0, 33] | 0 [0, 33] | 0 [0, 33] | 0 [0, 33] |
| Insomnia | 33 [0, 33] | 33 [0, 66] | 33 [33, 66] | 33 [0, 33] | 33 [0, 50] | 33 [0, 33] |
| Appetite loss | 0 [0, 0] | 0 [0, 33] | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] |
| Constipation | 0 [0, 0] | 0 [0, 33] | 0 [0, 0] | 0 [0, 33] | 0 [0, 33] | 0 [0, 33] |
| Diarrhea | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] |
| Financial difficulties | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] | 0 [0, 0] |
| Global quality of life | 83 [66, 91] | 83 [66, 83] | 83 [66, 83] | 83 [66, 83] | 79 [62, 83] | 75 [58, 83] |

Data are median [interquartile range]

*TAM* tamoxifen, *AI* aromatase inhibitors, *QLQ-C30* quality of life-C30

motor attention, and manual dexterity was also found in post-menopausal BC patients treated with tamoxifen or anastrozole and compared to healthy age-equivalent controls [30]. Nevertheless, in these studies, no between-group analyses were available to determine whether tamoxifen, anastrozole, or a combined treatment was implicated and no pretreatment baseline assessment was performed. In a smaller cohort, Bender et al. reported poorer results in verbal and visual learning and memory tests in early-stage BC patients treated with anastrozole compared to tamoxifen users [9]. Nevertheless, in the Ibis II study, no cognitive difficulties were observed in post-menopausal women at increased risk of BC taking anastrozole compared to the placebo group after 6 months and 2 years of treatment [31]. The impact of exemestane on cognition has been less frequently evaluated. In the TEAM (tamoxifen and exemestane adjuvant multinational) trial, neuropsychological assessments were performed at baseline and at 1 year. While no impact of exemestane on cognition was found, tamoxifen users had poorer performances than healthy controls on verbal memory and executive functioning [8].

Our population was a post-menopausal population who already experienced a progressive hypo-estrogenic condition, which could have minimized the effects on cognitive function by tamoxifen or AI as suggested by other authors [32], or could result in less competition for binding sites with tamoxifen [33]. Our findings thus cannot be generalized to a younger population.

In our study, no specific differential effect between tamoxifen and AI was found. Nevertheless, the absence of identification of an objective impact of hormonotherapy during the cognitive evaluation cannot exclude subtle neuropsychological disorders that are not measurable using standard tests. Subjective perceived deficits may be reported by patients, especially at work or when a high level of concentration is needed, while standardized neuropsychological assessments conclude that functioning is normal [25, 34, 35]. In other studies, the relationships between perceived cognitive function and objective measures are not consistent, even though no correlation is more frequently found [7, 27, 36–38]. In our study, tamoxifen users reported less cognitive impairments in daily living on the CDS than AI users at baseline. Although cognitive complaint increased in both groups compared to baseline, no difference was then observed between the groups during follow-up. Furthermore, the scores were not significantly different between the arms for the QLQ-C30, IADL, and HADS questionnaires at baseline or during follow-up. Completion rates for the QLQ-C30 were of 89 % at

baseline, 67 % for the 6-month visit, and 75 % for the 1-year visit (see Table 3) and analyses on these scores should thus be interpreted with cautious. However, as in our trial, quality of life, measured by the EORTC, QLQ-C30, and the Short Form-12, was similar in both tamoxifen users and AI users in another study [39]. Mood modulation may be a potential mechanism to explain cognitive difficulties [40, 41]. For most authors, cognitive complaints can be related to mood (anxiety or depression) and/or fatigue [7, 27, 36–38, 42–45]. Cognitive deficits have been observed in BC patients after surgery and before chemotherapy initiation, as what was observed in our trial. When looking at individual performances of our BC patients, we found around 34 % of patients presenting with a deficit for an executive task (trail making test) and 29 % presenting with a deficit on verbal working memory scores. These deficits were stable across the trial and thus did not evidence any effect of the endocrine therapy instauration. These early cognitive deficits have been frequently attribute to the impact of stress on cognition [46–48]. Nevertheless, only moderate correlations were reported between self-reported cognitive functioning and anxiety, depression, fatigue, or menopausal complaints in patients enrolled in the TEAM study [49]. Depression has also been reported to be associated with a lack of estrogen or failure of estrogen to bind with its receptors [50, 51]. Nonetheless, no difference was found in our study between tamoxifen and AI users on an emotional scale.

Some limitations of the current study should be noted. Although the study was a non-double-blind study, neuropsychologists were blinded to the treatment arm of the patient. No functional or metabolism cerebral imaging was performed during the study to evaluate the recruitment of cortical areas in these patients. Patients were followed only for 1 year, and thus we cannot exclude potential long-term effects of hormonotherapy in this population of patients, despite the fact that most of the adverse effects of AI occur in the first year of treatment [31]. In this study, the goal was to evaluate the differential impact of tamoxifen and AI on cognitive functions. No control group was tested, and thus we cannot conclude on the precise impact of hormonotherapy on cognition. The use of a control group without BC would have been questionable because of the interaction between cognition and breast cancer itself and its consequences (such as mood and fatigue). Moreover, we compared the impact of tamoxifen versus AI, considering that the impact of AI on cognition has a class effect due to the severe deprivation of estrogen. No standard does exist to recommend a specific AI agent in adjuvant therapy, and the choice was left to the referring oncologists of the patients. Nevertheless, different relationships have been reported between anastrozole, exemestane or letrozole, and cognition. In different studies comparing AI to tamoxifen, greater cognitive impairments were usually described with anastrozole compared to exemestane or letrozole [8, 9, 31, 32, 52, 53]. These results may be partially explained by the inconsistency in the methodology between the trials but also by different pharmacological effects of the third generation AIs. Mild androgenic properties of exemestane and its metabolites, which could preserve cognitive function, have been reported [54, 55]. Letrozole could be a more potent inhibitor of aromatase than anastrozole, leading to distinct effects [56]. Furthermore, interactions of these treatments with a history of post-menopausal hormone therapy have been previously described on cognitive complaint of BC patients, especially for patients receiving AI [25]. Unfortunately, these data were not available in our population but should be considered in future research. A standard questionnaire on symptoms related to menopausal status or side effects of endocrine therapy should also be considered in this perspective to define their interaction with cognitive impairment in this population.

## Conclusion

This trial did not demonstrate a significant difference between baseline and 6-month scores on the RAVLT in tamoxifen versus AI-treated post-menopausal early BC patients. Altogether, our study suggests that cognitive functions as well as emotional and quality of life measures are not influenced by the choice of the agent of hormonotherapy in the tested population.

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**Complaince with Ethical Standards**

**Conflict of interest** The authors have no conflict of interest to declare.

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