Effects of tamoxifen and exemestane on cognitive functioning: a study in postmenopausal breast cancer patients

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Chapter 8

Summary of results and general discussion

Introduction

In this chapter, the aims and main conclusions of the studies are presented. In addition, several methodological issues that have arisen from the studies will be discussed. The chapter concludes with issues regarding the interpretation of the findings, implications for clinical practice and recommendations for future research.

Aims of the thesis

The primary aim of this thesis was to investigate the impact of two types of adjuvant endocrine treatment, tamoxifen and exemestane, on cognitive functioning in postmenopausal breast cancer patients. Endocrine treatment is an important option for patients with hormone-sensitive breast cancer. For decades, tamoxifen (a selective estrogen receptor modulator [SERM]) was the standard adjuvant endocrine treatment for post-menopausal women. The use of 5 years of tamoxifen is associated with a 41% relative risk reduction of recurrence of breast cancer and a 34% relative risk reduction of death in patients with hormone-sensitive breast cancer.[1] The advantage of 5 years of tamoxifen over no adjuvant treatment persists even after a follow-up period of 15 years.[2] More recently, several clinical trials showed that including an aromatase inhibitor (AI) in adjuvant endocrine therapy, for example anastrozole, letrozole or exemestane, further improves survival.[3] Ongoing trials are exploring the optimal duration of adjuvant endocrine therapy, as well as the most effective choice and sequence of agents.[4] Although generally well tolerated, endocrine treatments have side effects which are of clinical concern[5] and are predictive of non-adherence to the treatment regimen.[6] Many side effects of endocrine therapy, such as hot flashes and mood disturbances, are related to estrogen deprivation and are common to tamoxifen and AIs. In addition, tamoxifen has estrogenic effects that are beneficial in some tissues: tamoxifen lowers serum cholesterol levels and protects against bone loss and cardiovascular disease, but is also associated with a higher risk of endometrial cancer and thromboembolic disease. AIs are associated with a lower incidence of gynecological symptoms and hot flashes than tamoxifen.[7] However, AIs are associated with musculoskeletal side effects, such as arthralgia, myalgia and bone loss.[7]

The rationale behind this study, specifically focusing on potential effects of endocrine treatments on cognitive functioning, can be found in the increasing evidence that estrogens are important for cognitive functioning.[8] This raised questions about possible detrimental effects of endocrine treatments for breast cancer, which aim at estrogen deprivation, on cognitive functioning.[9] Evaluation of possible effects of endocrine treatments is relevant, because intact cognitive functioning is important for wellbeing and independent living of patients. The randomized Tamoxifen and Exemestane Multinational trial (TEAM trial) provided the opportunity to study the effects of two different types of endocrine treatment, the SERM tamoxifen and the AI exemestane on cognitive functioning in a prospective way.

The prospective design included baseline cognitive assessments. This enabled us to evaluate cognitive functioning after surgery, but before the start of adjuvant endocrine treatment. This is important because several prospective cognitive studies in breast cancer patients reported cognitive impairment that was already present before the start of adjuvant systemic treatment.[10,11] Up till now, the origin and extent of this pre-treatment cognitive impairment are unclear. Possible explanations postulated in the literature include the impact of psychological distress[12] on cognitive functioning, or negative effects of anesthesia and surgery undergone in the weeks before the baseline cognitive assessment.[13] The extent to which pre-treatment cognitive impairment is observed might also be dependent on the methodology used to describe cognitive performance. A secondary aim of this thesis was to increase the understanding of cognitive functioning prior to adjuvant systemic (endocrine) treatment. We evaluated the pre-treatment cognitive functioning from two different points of view: first, we targeted methodological aspects regarding the use of pre-defined criteria for cognitive impairment and the choice of a reference group (published normative data versus a study-specific healthy control group). We classified participants as 'cognitively intact' or 'cognitively impaired' according to different criteria for cognitive impairment and different reference groups in order to highlight the contrasting results of these different methods. Secondly, we compared, at a group level, cognitive functioning of postmenopausal breast cancer patients before the start of endocrine treatment with that of healthy controls and evaluated to what extent medical and psychological factors explained the differences in cognitive functioning between breast cancer patients and healthy controls.

A growing number of patients receive endocrine treatment after completion of chemotherapy. The TEAM trial also provided the opportunity to evaluate cognitive functioning in breast cancer patients who were exposed to both chemotherapy and endocrine treatment. We did this in an additional, cross-sectional study in which we compared cognitive functioning of patients who received tamoxifen with patients who received exemestane after treatment with doxorubicin/cyclophosphamide (AC) chemotherapy. Furthermore, we pooled the tamoxifen and the exemestane groups into one patient group and compared cognitive functioning in this combined patient group with that of healthy controls.

In order to obtain a more complete picture of the possible influence of endocrine treatments on cognitive functioning, we included 'patient-reported outcomes' (PROs) on cognitive functioning in addition to cognitive test performance. PROs are measurements of aspects of a patient's health status that come directly from the patient without interpretation of the patient's response by a clinician or anyone else. They are particularly important in clinical trials in which two treatments with similar efficacy may have different safety profiles that have an impact on patients' symptoms, functioning, or health-related quality of life (HRQoL). PROs may complement and extend information provided by clinical end points on the efficacy and side-effects of treatment. [14] In this thesis, PROs were used to evaluate self-reported cognitive functioning in tamoxifen users, exemestane users and healthy control women, and to evaluate associations between self-reported cognitive functioning and cognitive test performance. Because it is known from the literature that symptoms of anxiety/depression, fatigue and menopausal complaints might play a role in both self-reported cognitive functioning and cognitive test performance, the associations of self-reported cognitive functioning with these variables also were evaluated.

Synopsis of the key findings

Chapter 2 provides a summary of the literature about the possible effects of estrogens and endocrine therapy for breast cancer on cognitive functioning in aging women. The effects of estrogens on cognitive functioning in aging women have been evaluated in numerous studies. The results of these studies indicate that the natural menopausal transition is not, or at the most, weakly associated with cognitive decline. On the contrary, surgical menopause has an effect on verbal memory functioning coincident with changes in plasma estrogen levels, indicating that abrupt lowering of estrogen levels is associated

with cognitive decline. Studies that evaluated the effects of hormone replacement therapy (HRT) on cognitive functioning also provide evidence for cognitive effects of estrogen. Summarized, these studies provide evidence for beneficial effects when HRT is administered in the years close to the menopausal transition, but for no, or even detrimental effects when administered many years after menopause.[15,16] Although the nature of the possible effects of estrogens on cognitive functioning is becoming more apparent due to extensive study in recent years, the potential effects of endocrine therapies for postmenopausal breast cancer patients, aiming at estrogen deprivation, on cognitive functioning have only been evaluated to a limited extent. Studies evaluating tamoxifen suggest small detrimental effects on cognitive functioning[17-19], while studies on anastrozole (the only AI for which cognitive data are available) report conflicting results with regard to its effect on cognition.[18-21]

In **Chapters 3 and 4**, two studies with regard to cognitive functioning *before* the start of endocrine treatment are described. One of the methods to investigate cognitive functioning is to classify the participants as 'cognitively impaired' or 'cognitively intact' according to a pre-defined criterion and compare the proportion of 'cognitively impaired' patients with the proportion found in a reference group. In the literature regarding cancer and cognition many different criteria, as well as different types of reference groups are used, resulting in substantial differences in the observed prevalence of cognitive impairment leaving questions on actual percentages of patients affected unanswered.[22] In **Chapter 3**, the impact of four different criteria for cognitive impairment (failure on ≥4, ≥3, ≥2 and ≥1 tests respectively) and two types of reference groups (our own study-specific healthy reference group versus published normative data) on the prevalence of cognitive impairment was examined. The patient group consisted of 205 postmenopausal breast cancer patients (mean age 68.9 years) who were about to start with endocrine treatment. The study-specific healthy reference group consisted of 124 postmenopausal friends and relatives of the patients (mean age 66.5 years). The prevalence of cognitive impairment varied greatly with the strictness of the criterion, as expected, but also was dependent on the reference group used. Cognitive impairment, relative to published norms, ranged from 1% for the most strict to 36.6% for the least strict criterion. Cognitive impairment relative to study-specific healthy controls, ranged from 13.7 to 45.4% for the same criteria. This study highlights the contrasting proportions of patients classified as 'cognitively impaired' by using different criteria for cognitive impairment and different reference groups.

Furthermore, it stresses the need for consensus on the measures and statistical methods to study cognitive impairment both before and during/after adjuvant systemic therapy.[23]
The second study (**Chapter 4**) aimed to identify medical and psychological predictors for cognitive performance of breast cancer patients before the start of adjuvant systemic treatment, and to compare cognitive test performance between breast cancer patients and healthy controls adjusting for medical and psychological variables. In this chapter, we analyzed the data of the same group of patients (n=205, mean age 68.9 years) en healthy controls (n=124, mean age 66.5 years) on a group-level. We found that 'treatment for diabetes mellitus' and/or 'hypertension', 'less hours spent on cognitively stimulating activities', 'fewer days since surgery' and 'more reproductive years' were associated with lower cognitive performance in the breast cancer patients, independent of age and IQ. These medical and psychological variables explained a modest 1-6% of the variance in addition to the 10-40% of the variance explained by age and IQ. Cognitive differences between breast cancer patients and healthy controls could partially be explained by the evaluated variables, but a small-to-medium unexplained difference remained. The results stress the need for adjustment for pre-treatment cognitive differences between study groups, and also indicate that further research into the cause of pre-treatment cognitive dysfunction is warranted.

Chapter 5 describes the core study of this thesis, a prospective neuropsychological study involving 38 hospitals in the Netherlands investigating the effects of tamoxifen and exemestane on cognitive functioning of postmenopausal breast cancer patients who had not received chemotherapy. Patients were TEAM trial participants who were randomized between tamoxifen (n=80, mean age = 68.7 years) or exemestane (n=99, mean age 68.3 years) after surgery with a curative intent. All patients underwent neuropsychological examinations before the start of tamoxifen or exemestane treatment (T1), and after one year of continuous treatment (T2). In order to take practice effects, which are inherent to neuropsychological testing, into account, a healthy control group consisting of friends and relatives of the patients underwent the same tests twice at an interval of 1 year. Eight cognitive domains were created out of 18 test indices. After one year of treatment (T2) and after adjustment for T1 performance, exemestane users did not perform statistically significantly worse than healthy controls in any cognitive domain. In contrast, tamoxifen users performed statistically significant worse than healthy controls on verbal memory and executive functioning and statistically significantly worse than exemestane users on

information processing speed. With respect to visual memory, working memory, verbal fluency, reaction speed and motor speed, no significant differences between the three groups were found. All effect-sizes were in the small-to-medium range.

In clinical practice, many patients who receive endocrine treatment also received treatment with chemotherapy in the past. From previous research at the Netherlands Cancer Institute and in other research groups it is known that chemotherapy might be associated with cognitive impairment in a subgroup of patients[24-26], depending on the specific regimen applied. To explore the impact of chemotherapy, followed by tamoxifen or exemestane on cognitive functioning, we performed a cross-sectional study described in **Chapter 6**. In this study, TEAM trial patients who received standard-dose adjuvant chemotherapy before the start of endocrine treatment participated. The patients were randomized between tamoxifen (n=30, mean age 57.9 years) or exemestane (n=50, mean age 58.5 years) after doxorubicin/cyclophosphamide (AC) chemotherapy and completed chemotherapy on average 2 years before the neuropsychological assessment. In addition, a reference group consisting of healthy women of approximately the same age was included (n=48, mean age 60.2 years). These healthy women were selected from the prospective study (see Chapter 5) on the base of the age and IQ distribution of the patients. On 18 measures of cognitive functioning, patients receiving tamoxifen were compared with patients receiving exemestane, and the combined patient group was compared with the healthy reference group. Cognitive testing revealed no statistically significant differences between tamoxifen and exemestane users, but suggested that tamoxifen use is possibly related to worse verbal functioning, while exemestane use is possibly related to slower manual motor speed. Both patient groups performed significantly worse than healthy controls on tests of verbal fluency and information processing speed. This study showed that sequential treatment of AC-chemotherapy and hormonal therapy in postmenopausal breast cancer is associated with lower test scores for certain cognitive functions, and provides indications of possibly distinctive associations for different types of hormonal treatment. No correlations between cognitive performance and anxiety/depression ratings were observed. Memory *complaints* (defined as having a frequency of at least 'regularly') were reported by 28% of AC/tamoxifen users, 24% of AC/exemestane users and 6% of healthy controls.

The study described in **Chapter 7** focuses on self-reported cognitive functioning of breast cancer patients who use tamoxifen or exemestane. We aimed (1) to evaluate self-reports on cognitive functioning of postmenopausal breast cancer patients undergoing adjuvant endocrine treatment with tamoxifen or exemestane compared to healthy controls, and (2) to explore associations between self-reported cognitive functioning, cognitive test performance, anxiety/depression, fatigue and menopausal complaints. The participants were the same as in the core-study of this thesis (Chapter 5): TEAM trial participants who were randomized between tamoxifen (n=80, mean age = 68.7 years) or exemestane (n=99, mean age 68.3 years) after surgery with a curative intent. They provided data on self-reported cognitive functioning (both interview data regarding cognitive complaints as questionnaire data regarding the frequency of everyday cognitive failures and lapses). Furthermore, they provided questionnaire data on anxiety/depression, fatigue and menopausal complaints, and underwent cognitive assessments before (T1) and after one year (T2) of adjuvant endocrine treatment. Identical information was obtained from healthy postmenopausal volunteers (n=120). At T1, the three groups did not differ significantly with regard to the prevalence of self-reported cognitive complaints. At T2, adjusted for complaints at T1, the prevalence of *concentration,* but not of *memory* complaints differed significantly between the groups, due to an increase among tamoxifen users. The frequency of reported cognitive failures was not different between groups at T2, adjusted for T1 scores. Cognitive test performance was not associated with self-reported cognitive functioning. Self-reported cognitive functioning showed moderate associations with anxiety/depression, fatigue and menopausal complaints. Cognitive test performance was weakly associated with anxiety/depression and fatigue. Our results indicate that self-reports on cognitive functioning can not be regarded as substitutes for cognitive test performance, but might be more indicative for the level of, among others, anxiety/depression and fatigue.

Methodological considerations

This paragraph discusses the major methodological strengths and weaknesses of the study in more general terms.

Participation rate

Recruiting participants for clinical and neuropsychological studies is often a difficult task. Low participation rates undermine statistical power, increase the probability of bias and limit the ability to generalize the results. Loss of eligible patients may occur in several ways: patients may be recruited selectively, and patients may decline participation.

As in many studies in the social sciences, potential loss of eligible patients was a threat in our study. Selective recruitment of patients might have occurred on two occasions: (1) the physicians might have asked patients selectively for participation in the TEAM trial and (2) the physician might have asked patients selectively to participate in the neuropsychological side study. On three occasions, patients could actively decline participation: they could decline participation in the TEAM trial itself (3), they could decline participation in the neuropsychological side study (4) and they could decline participation in the follow-up measurement (5).

With respect to selective recruitment (occasion 1) and active decline of patients for the TEAM trial (occasion 3) no data are available. In the case of occasion 2, 53 of the 393 eligible patients were missed due to starting problems or other organizational problems in the hospitals, or because the oncologist found them not suitable for the study (n=9) due to, for example advanced age (n=2) or, interestingly, cognitive dysfunction (n=3). Of the 331 patients who were asked to participate in the neuropsychological side study, 125 (38%) actively declined participation (occasion 4). A factor that might have played a role in the less than optimal participation rate is the way in which participation was requested. Our intent was for oncologists and research nurses to only briefly introduce the study to eligible patients, hand over an information leaflet and ask for the patient's permission to be called by the researchers. In a subsequent telephone call we would provide more information about the study and patients could then decide whether or not to participate. In practice this way of recruiting patients did not work well. Despite our repeated instructions to the hospital and the datacenter, we only received contact information for patients who already had decided to participate. We did not have the opportunity to get

in touch with the other patients to provide additional information or answering questions, which potentially would have influenced their decision to participate.
Finally, loss to follow-up (declining on occasion 5) was limited to 13% of the patients.

The participation rate of the cross-sectional study among breast cancer patients who received chemotherapy before their participation in the TEAM trial was 85%, higher than for the prospective study. One of the reasons for this higher participation rate could be the fact that we contacted the patients directly, circumventing possible loss of participants on occasion 2. Other reasons might be the younger age of the patients, the fact that less effort was required (one assessment instead of two) and the fact that they were asked in a less overwhelming situation (2-4 years after the diagnosis) than the patients who were eligible for the prospective study.

The participation rate of the healthy control women is unknown because they were recruited by the participating patients, and we had no information about the number of friends and relatives that declined participation. Loss to follow-up was limited to 3% of all participating healthy control women.

To what extent were participation rates and loss to follow-up a threat for the potential to generalize of our study results? Especially when attrition of patients is not random, the probability of non-intended selection of participants is high. From the available data, we can conclude that a considerable number of patients (n=53) was missed due to organizational problems in the hospital, such as problems with starting up the inclusion procedure, high work-load or loss of interest on the part of physicians. As this loss of potential patients might be predominantly random, the amount of bias introduced is probably limited. The nine patients who were missed because their physician considered them unsuitable for the study might have introduced some bias, as it concerned mostly old and cognitively frail patients. The participation rate of TEAM trial participants who were asked to participate in the neuropsychological side study (respectively 62% and 85%) is comparable to similar studies, but participating patients might represent a non-intended selection of patients, for example patients who were in relatively good health, interested in the topic or are at ease with cognitive testing. We tested for possible age differences and concluded that there were no age-differences between the participants and non-participants. With respect to the healthy control group, some degree of selection bias

might be introduced as the patients, in general, tended to invite a relatively young and healthy friend or relative (mean age of patients 68.9, of healthy controls 66.5 years of age).

Loss to follow-up in our prospective study was limited to 13% of the patients and 3% of the healthy controls, which is an important strength of our study. Nevertheless, loss to follow-up seemed not to be completely random, as participants who were lost to follow-up were significantly older (72.3 versus 67.6 yrs; *P*=<0.01) and had a lower IQ (93.9 versus 102.7; *P*=0.02) than participants who completed both assessments.

In summary, the participation rate in our studies was suboptimal and non-participation was not completely random, as participants might be healthier and more interested and more at ease with cognitive testing than non-participants. Probably, this induced some degree of bias, which limits the ability to generalize of the results. For future studies, it is recommended to increase the possibilities to control the inclusion of patients and healthy controls, for example by the ability to contact all eligible participants directly, and monitoring the inclusion process of the healthy controls.

Sample size and statistical power

Given the knowledge derived from previous studies on the effects of estrogens and anti-estrogenic treatment on cognitive functioning, large cognitive effects of endocrine treatment are not to be expected. Therefore, studies need relatively large sample sizes in order to have satisfactory statistical power. The sample size of our prospective study (80 tamoxifen users, 99 exemestane users and 120 healthy controls) was large compared to other neuropsychological studies with cancer patients. We had a statistical power of at least 76% to detect differences in test scores of 0.4 standard deviations between the groups. Our sample sizes in the cross-sectional study among TEAM trial participants who received chemotherapy before the start of endocrine treatment were smaller (30 tamoxifen users, 50 exemestane users and 48 healthy controls). The lack of statistically significant differences between the tamoxifen- and the exemestane group on cognitive functioning might thus be a result of the insufficient statistical power to detect differences.

Randomized study with additional healthy control group

The randomized character of the TEAM trial, in which breast cancer patients were randomly allocated to tamoxifen or exemestane, resulted in two patient groups in which important confounding factors such as age and age-related comorbidity, socio-demographic background and prognosis were well balanced. The healthy control group, included in the study in order to take into account test-retest effects, was not composed in a randomized way. We chose for a control group consisting of healthy female friends and relatives of the patients in order to minimize differences in social and cultural background between patients and controls. A drawback of this non-randomized control group is the possible introduction of known and unknown sociodemographic, medical and psychological differences between the patients and the healthy controls, which might be of influence on cognitive functioning. Although we collected information about many potentially important variables and used statistical procedures in order to take into account the cognitive differences that were present before the start of endocrine treatment, the question remains whether such a statistical adjustment was sufficient to manage the pre-existing cognitive differences completely.

Prospective study

Our main study (Chapter 5) had a prospective design. An important strength of a prospective study is the possibility to study causal relationships and to study changes over time. Nevertheless, the determination of a causal relationship between different treatments and cognitive functioning might be problematic because other variables that could influence cognitive functioning might change simultaneously in the year between the first and second assessment. In this study such variables could be related to the diagnosis of cancer and other treatments, changes in health, changes in (prescription) medications, important life events etc. We were able to adjust for several variables that appeared to have changed over time in the patients and healthy controls, i.e. anxiety/depression, fatigue and menopausal complaints. These adjustments did not change the results, suggesting that these variables did not drive the relationship between the endocrine treatment and cognitive functioning.

Selection of cognitive domains and cognitive tests

At the time this study was started, the topic of cognitive effects of endocrine treatment for breast cancer had hardly been studied. In the few published neuropsychological studies at that time, only very small test batteries (2 or 3 tests) were used. These tests represented a diversity of cognitive domains, but a rationale for the cognitive domains of choice was not given. For the selection of the cognitive tests used for this thesis, we referred to the literature about effects of estrogens on cognitive functioning. The literature provided some evidence that the influence of estrogen on cognitive functioning is restricted to several specific cognitive domains, such as verbal memory, information processing speed and aspects of executive functioning.[27] An appropriate selection of test should include tests covering these domains. However, consensus about the cognitive domains that are exclusively vulnerable to the effects of estrogen or endocrine treatment for breast cancer was lacking. In order to make sure inclusion of all relevant cognitive domains, we composed a battery of tests that covered a wide range of cognitive domains.

Selection of Patient-reported outcomes (PROs)

Self-reported cognitive functioning

In addition to the neuropsychological tests, we used several measures for self-reported cognitive functioning. Because no consensus exists in the literature about the best way to assess self-reported cognitive functioning, we used two distinctive measures. First, we interviewed all participants about the presence of complaints regarding memory, concentration, thinking and language. If a complaint in a particular domain was present, we asked the participant to give examples, and to provide indications about the frequency of complaints and the extent the complaint hindered them in daily life. This semi-structured interview was used earlier in cancer populations to compare the prevalence of cognitive complaints between groups of cancer patients who underwent different treatments.[24] Secondly, we used the Broadbent cognitive failure questionnaire, a 25-item questionnaire measuring (on a 5-point scale) the frequency of everyday cognitive failures or lapses.[28] These concern failures on memory, attention, action and perception. This measure has been evaluated as having good internal consistency, retest reliability and face validity in a cohort of older adults. [29]

Anxiety/depression, fatigue and menopausal symptoms

We selected several self-report questionnaires to gather important quality of life information. Because these variables may act as covariates in the analyses of self-reported cognitive functioning and cognitive test performance, such information was important to obtain. For the measurement of symptoms of anxiety/depression the 25-item Hopkins Symptom Checklist (HSCL-25) was used, a sensitive case finder of clinically important depressive states in elderly populations.[30] For fatigue, the 3-item fatigue subscale of the EORTC QLQ-C30 was used. This subscale has been shown to be a reliable and valid measure of fatigue in clinical research settings.[31] Common side effects of endocrine treatment include menopausal symptoms. To investigate possible influences of menopausal symptoms on both self-reported cognitive functioning and cognitive test performance, we included the FACT-B Endocrine symptoms questionnaire, a reliable and valid questionnaire that is sensitive to clinically significant change.[32]

Choice for statistical method to evaluate prospective data

The prospective study (Chapter 5) included three groups (tamoxifen users, exemestane users and healthy controls) and two measurements (patients had cognitive assessments before the start of treatment and after one year of treatment, healthy controls were assessed twice at an interval of 1 year). The patients were randomly allocated to either tamoxifen or exemestane, but the healthy control group was not selected on the basis of randomization. In a design with two or more groups and two repeated measurements, different statistical approaches are possible. The neuropsychological literature did not provide clear guidance on a choice between the approaches. The two most common statistical approaches are: (1) analysis of variance (ANOVA) of the change from the baseline, defined as follow-up score minus baseline score, and (2) analysis of covariance (ANCOVA) with the follow-up score as the outcome and the baseline score as a covariate.[33,34] An advantage of the ANCOVA method over the ANOVA of change scores is that the ANCOVA method estimates the slope β, whereas the ANOVA of change scores assumes that the slope $\beta = 1$. In most situations, this ANCOVA method is regarded as more reliable and powerful than the ANOVA of change scores.[33,35] For both methods, however, homogeneity of regression slopes between the groups is assumed. We tested this assumption, concluded that it was not violated and chose for the ANCOVA method.

As stated before, a complicating factor was the mixed design with respect to the randomization. As a consequence, some comparisons were between randomized groups and other comparisons were between non-randomized groups. As baseline differences between the groups might result in differential bias in both methods[33], we analyzed our data with both methods in order to evaluate potential differences in the results. The ANOVA of change scores did not reveal different results from the ANCOVA, so we could maintain the ANCOVA approach in the knowledge that the results of both approaches were comparable.

Interpretation of findings

In the previous sections, the findings of the studies in this thesis are described, as well as some methodological considerations. We noticed that the non-randomized character of the healthy control group and the suboptimal statistical power, particularly in the cross-sectional study, were limitations in these studies. Nevertheless, given the clear advantages of these studies such as the comprehensive neuropsychological test battery, the choice of cognitive domains, the large number of self-report measures, the fact that the patients were randomized between tamoxifen and exemestane treatment, the results of all studies together give a good approximation to be discussed in terms of their meaning and their potential origin.

Differences between effects of tamoxifen and exemestane on cognitive functioning

At the time that we started this study, the evidence for beneficial effects of estrogen on the brain and on certain cognitive functions was increasing. AIs, such as exemestane, almost completely inhibit the action of the enzyme aromatase, which is required for the peripheral conversion of androgens into estrogens.[36] Consequently, AIs lower the level of circulating estrogen by almost 100%.[37] Based on the putative beneficial effects of estrogens on cognitive functioning, together with the fact that exemestane lowers estrogen levels almost to zero, we hypothesized a detrimental effect of exemestane on cognitive functioning, which might be limited to certain cognitive domains.

Tamoxifen's mechanism of action differs from that of the AIs. Tamoxifen binds to estrogen receptors, but whether its action is estrogenic or anti-estrogenic depends on the tissue. For example, on breast tissue, tamoxifen exerts anti-estrogenic effects, while on bone or

endometrial tissue, tamoxifen has estrogenic effects. It is not known whether tamoxifen has specific estrogenic or anti-estrogenic effects on brain tissue, hampering the possibility to formulate hypotheses about the effects of tamoxifen on cognitive functioning. The limited literature about cognitive effects of tamoxifen indicated small negative effects[17-20]. Based on the existing literature, we hypothesized detrimental effects on cognitive functioning for tamoxifen, and again, potentially limited to certain cognitive domains, for example verbal memory.

We could not formulate hypotheses about differences in cognitive effects between tamoxifen and exemestane, although we could not rule out cognitive differences because of the different mechanisms of action of both agents. Possible differences in cognitive effects between the two agents were investigated in an exploratory/hypothesis-generating way.

With respect to exemestane, our hypothesized negative cognitive effects were not confirmed by our findings. This indicates that in postmenopausal breast cancer patients, lowering of estrogen levels does not result in measurable cognitive effects. Another explanation might be found in the mild androgenic properties of exemestane.[38] Because androgens might be beneficial for performance in several cognitive domains[39], detrimental effects on cognitive function of estrogen deprivation might be limited, or even prevented by the androgenic properties of exemestane. Future head-to-head comparison of the cognitive effects of exemestane and other AIs that have no androgenic properties (for example anastrozole and letrozole) will be important in order to determine whether the absence of cognitive effects of exemestane is specific to this drug, or is a property of all AIs. A difference in cognitive effects between different AIs has potential implications for clinical practice.

With respect to tamoxifen, our results confirm our hypothesis of detrimental effects on certain cognitive domains (i.e. verbal memory and executive functioning). Based on the assumption that estrogens are beneficial for cognitive functioning, one might conclude that tamoxifen acts as an anti-estrogen on brain tissue. But, as it is questionable whether estrogens are beneficial for cognitive functioning in older women (>65 years of age)[40], one might also conclude that tamoxifen has estrogenic effects on the brain, at least in older women. So, in spite of the consistent finding of detrimental cognitive effects of tamoxifen

in studies conducted up to now, including this study, these results do not provide clues to the mechanisms of action of tamoxifen in brain tissue. Animal models might provide insight into these mechanisms of action. Potential mechanisms to evaluate in future research should include the effects of tamoxifen on the two estrogen receptors, ERα and ERβ, in the brain. Since estrogens may have different effects on ERα and ERβ[41], which are also differentially expressed in various parts of the brain[42], this distinction might be relevant for tamoxifen as well. Additionally, tamoxifen may act as an antagonist *and* as an agonist of ERs, or via mechanisms that are independent of genomic actions. In addition, age should be taken into account in animal studies as age is a factor of possible importance regarding the effects of endocrine treatments on the brain.

Cognitive performance before the start of adjuvant therapy, do different statistical methods lead to different results?

Two chapters in this thesis describe cognitive functioning before the start of endocrine treatment, each from a different point of view. In **Chapter 3**, methodological issues are discussed regarding, among others, the use of predefined criteria for cognitive impairment based on the number of tests failed. In **Chapter 4**, cognitive differences were evaluated by comparing mean cognitive scores between the breast cancer patients and the healthy controls. Although **Chapter 3** focuses on methodological issues and did not aim to judge cognitive performance of breast cancer patients compared to healthy controls, one might conclude from these data that the cognitive performance of breast cancer patients was comparable to that of healthy controls, as the two groups were not significantly different with respect to the proportion of individuals who were classified as 'cognitively impaired'. On the contrary, in **Chapter 4**, the results showed a statistically significantly lower overall cognitive performance of breast cancer patients compared to healthy controls.

The two studies were based on exactly the same data but revealed divergent results, demonstrating that the conclusions are dependent on the statistical method used. The extent to which methods using criteria and methods comparing mean test scores between groups will produce different results, depends on, among other factors, group size and the distribution of test scores within the group. Both types of analyses are widely used in the neuropsychological literature, separately or combined.[25,43] In general, the analysis of mean cognitive scores has the advantage that the complete range of scores on a test is used without loss of information as a result of the classification. Data of proportions of

individuals with 'cognitive impairment' according to a particular criterion identify and highlight the individuals with the lowest scores. This might be justified in some cases, for example if there is evidence that only a specific subgroup, exclusive of the others, is cognitively affected. An important point of concern is that the compilation of such a subgroup is highly dependent on the nature and strictness of the criterion. Furthermore, the assignment of individuals to the 'cognitively intact' or 'cognitively impaired' subgroup might be influenced by confounding factors such as age, education, IQ, comorbidities etc. Therefore, it cannot be assumed that individuals in the 'cognitively impaired' subgroup, exclusive of the others, are actually the ones who are cognitively affected by the condition under study.

One of the aims of this thesis was to evaluate cognitive functioning of postmenopausal breast cancer patients before the start of endocrine treatment. No reason for identifying a specific subgroup of individuals exists in this situation. Therefore, comparing mean cognitive scores between patients and healthy controls, as is done in the study described in **Chapter 4**, is the preferred method. The study described in **Chapter 3** must be considered purely as a demonstration of the impact of different criteria for cognitive impairment and different reference groups on the observed prevalence. For the aim of this study, the use of the baseline cognitive assessment data was arbitrary.

Differences between effects of chemotherapy followed by endocrine treatment and endocrine treatment only

In this thesis, two studies with a focus on cognitive functioning in patients receiving tamoxifen or exemestane are described (**Chapter 5** and **6**). Due to many differences, the ability to compare these studies is limited. Among others, differences exist in the design (prospective versus cross-sectional, the latter lacking the possibility to adjust for pre-treatment cognitive differences); the size of the tamoxifen, exemestane and healthy control groups (80, 99 and 120 participants versus 30, 50 and 48 participants, the smaller study having less statistical power); prior adjuvant systemic treatment (no chemotherapy versus AC-chemotherapy); the age of the participants (roughly 68 versus 58 years of age) and time since diagnosis (roughly one versus three years). Furthermore, in the cross-sectional study raw test scores were compared between groups, whereas in the prospective study cognitive domain scores were created.

Nevertheless, if the results of both studies would point in the same direction, conclusions about the cognitive effects of both tamoxifen and exemestane increase in robustness. Therefore, we exploratory compared both studies with respect to the cognitive domains in which low scores or decreased scores were observed, disregarding statistical significance. We observed that, with respect to verbal memory, both studies report larger detrimental effects of tamoxifen than of exemestane. The same is true for most tests of executive functioning and information processing speed, although for two tests (Trailmaking A and B) the results are not congruent between both studies. The results of the cross-sectional study further suggest relatively large effects on reaction speed for both treatment groups which were not observed in the prospective study. The AC-chemotherapy, speculatively, might have played a role in the low scores for reaction speed. Finally, only in the cross-sectional study was a detrimental effect on verbal fluency observed for tamoxifen users.

In summary, the results of both studies point in the same direction in that they both suggest differential effects of tamoxifen and exemestane, and suggest larger and more widespread effects of tamoxifen on cognitive functioning compared to exemestane.

Implications for clinical practice and further developments

Associations between cognitive test performance and cognitive complaints, ecological validity of tests

In the studies described in this thesis no associations were found between self-reports of cognitive functioning and cognitive test performance. Our findings confirm the findings of earlier studies in cancer patients, as well as in other patient groups.[18,25,44-48] The lack of associations between self-reported cognitive functioning and cognitive test performance is a complex issue in neuropsychology. Intuitively, self-reported cognitive functioning and cognitive test performance should at least be related to a reasonable extent, because both are thought to be reflections of 'real world' cognitive functioning.

In the literature, the degree to which test performance corresponds to 'real world' performance (the 'ecological validity' of neuropsychological tests) receives increasing attention. In studies on the ecological validity of tests, associations between neuropsychological tests and outcome measures representing 'real world performance'

are investigated.[49] Examples of these outcome measures are: self-reports, checklists, informant-based questionnaires, clinicians' ratings, and observations of simulated activities.[49] Demonstrating the ecological validity of tests is complex, because it is influenced by many factors. Some of these concern the person who conducts the test or provides the information for the 'outcome measure' (for example personality characteristics[50], anxiety/depression[48], fatigue[51], illness severity[49], age, IQ and aptitudes[52], individual believes about someone's cognitive ability in different situations[53] and the demands of the professional and social situation relative to someone's cognitive capacities[54]). Besides these person-related factors the ecological validity of tests is influenced by the nature of the testing environment.[49]

A review of studies investigating the ecological validity of tests[55] demonstrated that the magnitude of associations between neuropsychological evaluations and measures of 'real world' cognitive skills was in the moderate range, and many individual tests were not, or only weakly related to outcome measures. A relatively robust conclusion was that, in neurologically impaired individuals, self-reports were more weakly correlated with neuropsychological examinations than clinician and informant ratings. In a recent study investigating the ecological validity of neuropsychological examinations[49], the neuropsychological examination itself could predict 30% of 'real world functioning' (as measured by interviews in which problematic daily life activities were identified and videotapes of participants performing these problematic activities). When neuropsychologists took additional information into account, such as observations of participants performing the tests, mood and neuropsychiatric symptoms, their ability to predict 'real world functioning' increased by another 30%.[49]

To conclude, 'real world' performance is poorly predicted by neuropsychological examinations only. The predictive value can be increased by adding information from other sources, for example mood or neuropsychiatric functioning. The use of self-reports as the only outcome measure of 'real world' performance has shortcomings too. Although self-reports of cognitive functioning are important in clinical practice, they are not the best outcome measures to determine the ecological validity of neuropsychological tests. In future research with cancer patients, the addition of other outcome measures may improve the ecological validity of neuropsychological examinations. For example, the outcome measure 'return to work' has been proved to be associated with cognitive test

performance in various patient groups.[56-58] Furthermore, other outcome measures, such as observations by informants or hospital/rehabilitation professionals, or memory diaries kept by the patient might provide additional information about cognitive problems that cancer patients might face in their everyday functioning.

For health care professionals, the weak associations between self-reported cognitive complaints and cognitive test performance might complicate the choice of further diagnostics and possible interventions for patients who express cognitive complaints. Patients with cognitive complaints are, after all, not necessarily the ones who have impaired cognitive test performance. However, these weak associations are observed in studies in which patients are actively approached by researchers and interviewed about possible cognitive complaints. It is possible that spontaneous cognitive complaints expressed by a cancer patient in a clinical setting have a different meaning than complaints that consist of responses to questions in a scientific study. In future studies, it should be determined whether associations between self-reported cognitive complaints and cognitive test performance are stronger in patients who express cognitive complaints spontaneously than in patients who participate in scientific studies.

Clinical relevance of findings

When the effect of a treatment on cognitive functioning is statistically significant, this does not automatically mean that this effect is also clinically relevant. Statistical analysis in clinical research is used to show that the findings are not likely due to chance. Clinical relevance merely focuses on the meaning and implications of the effect for patients and health care professionals. Although the exact meaning of the term 'clinical relevance' is dependent on the focus of the study, it is generally used to describe the magnitude of the effect, the extent to which the effect interferes with the daily life of patients or the extent to which useful recommendations for intervention can be provided.

Although this thesis provides evidence for statistically significant, negative effects of tamoxifen on several cognitive functions (verbal memory, executive functioning), the clinical relevance of this finding is not immediately obvious. As stated earlier, the degree to which neuropsychological test performance corresponds to 'real world' performance is limited in case no additional information is used, and self-reports of cognitive functioning are not the best predictors of 'real world' performance. Nevertheless, our results provide

several indications of clinical relevance. First, the small-to-medium magnitudes of the observed effects are not negligible. Further indications of clinical relevance are the consistence of our findings with earlier studies with respect to the cognitive effects of tamoxifen, the consistency of the cognitive domains found to be affected in our and earlier studies and the theoretical possibility of effects of tamoxifen on the brain.

An important suggestion from our results, and so far not described in the literature, is that the effects of tamoxifen on cognitive functioning are larger and more widespread in the older patients (65 - 85 years) compared to the younger patients (50 - 65 years). If this age effect is confirmed in future studies, this might have implications for clinical practice. The elderly are most at risk for cognitive deterioration. Cancer, treatments for cancer, comorbidities and several types of drugs (such as anxiolytics, sedatives and analgesics) can independently contribute to cognitive impairment in elderly breast cancer patients.

What can be concluded so far from our data with regard to clinical practice? Given the indications for clinical relevance listed above, it is recommended to take into account the potential cognitive effects of tamoxifen in the treatment decision-making process. In order to determine the optimum choice and sequence of the available endocrine agents from both an efficacy and quality of life perspective, all benefits and side effects should be considered and carefully weighted in the context of the individual patient and her comorbid conditions.

In elderly cancer patients, cognitive assessments are recommended. Such a cognitive assessment could be part of a Comprehensive Geriatric Assessment (CGA). This is a term coined by geriatricians to describe a multidisciplinary comprehensive evaluation of an older individual's functional status, comorbid medical conditions, cognition, psychological state, social support, nutritional status, and a review of the patient's medications. It has been demonstrated that the domains evaluated in a CGA can predict morbidity and mortality in older patients with cancer.[59-61] Incorporating a CGA in older patients at serial time points (prior to, during and after cancer treatment) can provide information regarding the short- and long-term impact of cancer therapy on cognitive functioning and other geriatric assessment variables. Other applications for the CGA, such as guiding interventions to improve the outcome in older cancer patients and the development of

novel end points for clinical trials that address quality of life and functional independence, are currently considered.[62]

Many questions relating to the clinical relevance of the cognitive effects of tamoxifen and exemestane remain unanswered in this thesis. For example, it is not known whether a longer duration of endocrine treatment would result in larger effects on cognitive function than the one year of treatment we investigated. Currently, two research projects have been initiated at the Netherlands Cancer Institute to evaluate the cognitive effects of a longer duration of endocrine treatment. First, all participants of the prospective study are invited for a third measurement after 4 to 5 years of endocrine treatment. With this study we will evaluate the effects of 4 to 5 years of exemestane, and the effects of 2 to 2,5 years of tamoxifen followed by 2to 2,5 years of exemestane on cognitive functioning. Secondly, a cross-sectional study has been started to evaluate cognitive functioning in postmenopausal breast cancer patients who receive tamoxifen for at least two years. Cognitive functioning of these patients will be compared with cognitive functioning of healthy controls, as well as with cognitive functioning of breast cancer patients who have not received endocrine therapy and/or chemotherapy. This 'breast cancer control group' has been added in order to restrict the extent of possible pre-treatment cognitive differences between the study groups since adjustment for pre-treatment cognitive differences is impossible in cross-sectional studies. Furthermore, it is unknown whether the cognitive effects of endocrine treatment are lasting after the treatment is finished. Knowledge about the stability or reversibility of cognitive effects may have important implications for clinical practice.

Information, diagnostics and interventions for cancer patients experiencing cognitive problems

While research is ongoing to unravel the complex issues with respect to cognitive problems associated with cancer and cancer treatments, in clinical practice health care professionals are sometimes faced with patients expressing questions or concerns regarding cognitive issues. A survey of nurses working at several departments in the Antoni van Leeuwenhoek Hospital revealed that 74% of the nurses reported being aware of the occurrence of cognitive problems associated with cancer or cancer treatment, 60% ever received questions from patients regarding cognitive functioning and 63% ever gave

information to patients about cognitive functioning in relation to cancer and cancer treatments.[63]

Evidence-based information, guidelines and treatments regarding cognitive functioning are scarce. There is a need for guidelines or a program in order to inform individual patients about cognitive problems associated with cancer and cancer treatment, to develop diagnostic tools to find the underlying cause(s), and determine ways for rehabilitation. Currently, at the Netherlands Cancer Institute, a short patient education program about cognitive problems related to cancer and cancer treatments is being developed. The program consists of an information pamphlet for patients and additional education for health care professionals about cognitive problems in relation to the type of treatment, time since diagnosis/treatment and possible associations with fatigue and psychosocial distress. The education program will also provide instructions for coping with complaints. In the future, specific interventions based on, among others, existing cognitive training/rehabilitation strategies for patients with brain damage and cognitive behavioral therapy for post-cancer fatigue may be helpful in improving the ability to compensate for cognitive problems.

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