



UvA-DARE (Digital Academic Repository)

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

Schilder, C.M.T.

Publication date
2010

[Link to publication](#)

Citation for published version (APA):

Schilder, C. M. T. (2010). *Effects of tamoxifen and exemestane on cognitive functioning: a study in postmenopausal breast cancer patients*. [Thesis, fully internal, Universiteit van Amsterdam].

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

Chapter **1**

General Introduction



General Introduction

Breast cancer is the most common malignancy in women in the Netherlands, with an incidence of 13.000 annually.¹ Due to more effective treatment, earlier diagnosis, and the introduction of a nationwide screening program in 1990, the prognosis of breast cancer has improved substantially.

Systemic treatments for breast cancer

Systemic treatments such as chemotherapy and endocrine therapy play an important role in the treatment of breast cancer in addition to loco-regional treatments such as surgery and radiation. In postmenopausal women, approximately 75% of the breast tumors are hormone sensitive.² For hormone-sensitive breast cancer, endocrine therapy is an important treatment option. Tamoxifen (a selective estrogen receptor modulator [SERM]) has been the standard adjuvant endocrine treatment for postmenopausal women for decades. More recently, several clinical trials showed that the inclusion of an aromatase inhibitor (AI) in adjuvant endocrine therapy, for example, exemestane, anastrozole or letrozole improves survival relative to treatment with tamoxifen only.³

Side effects of endocrine treatments

Endocrine treatments are aimed at estrogen deprivation by competitively binding to the estrogen receptor (ER), as is the case with the SERM tamoxifen or by interfering with estrogen biosynthesis, as is the case with AIs. Many side effects of endocrine therapy, such as hot flashes and mood disturbances, are related to estrogen deprivation and are common to both 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.⁴ AIs are associated with a lower incidence of gynecological symptoms and hot flashes than tamoxifen. However, AIs are associated with musculoskeletal side effects, such as arthralgia, myalgia and bone loss.⁴

Cognitive impairment as a known side effect of chemotherapy

Cognitive impairment, as reflected by memory and concentration problems, in cancer patients treated with chemotherapy for non-Central Nervous System (CNS) disease has received increasing attention in the last decade. The knowledge about this potential side effect of chemotherapy is growing⁵, and current research aims to further increase the understanding of the incidence, severity, risk factors, and causes of cognitive dysfunction, as well as to improve ways to prevent or minimize adverse symptoms.

Rationale behind the study of potential cognitive side effects of endocrine treatment

Cognitive impairment as a potential side effect of endocrine treatments for breast cancer has not been well studied. The rationale for a study into potential effects of endocrine treatments on cognitive functioning can be found in the increasing evidence that estrogens are important for CNS functioning and cognitive functioning.⁶ There are many hypotheses related to estrogenic effects on brain tissue and brain functioning, including estrogenic activity through receptors that are present in brain structures important for cognitive functioning, such as the hippocampi and the cerebral cortex.^{7,8}

Evaluation of the putative neuroprotective effects of estrogens in neuropsychological studies in women has led to partial support for a beneficial influence of estrogens on cognitive functioning. For example, estrogen deprivation following surgical removal of the ovaries in premenopausal women is associated with decreased verbal memory performance, while estrogen replacement therapy (ERT) is associated with stable cognitive performance in women who have had ovariectomies.^{9,10} In addition, a case-control study suggests that long-term estrogen deprivation following surgical menopause increases the risk of dementia later in life.¹¹

Harmful effects of estrogen on the brain, however, have also been described. In a large randomized, placebo-controlled trial, estrogen-containing hormone replacement therapy was associated with an increased risk of dementia and stroke in women over 65 years of age.^{12,13} This observation suggests that estrogens may only be neuroprotective during a critical time period around menopause and that estrogens offer no benefit to elderly women, in whom they may even have a detrimental effect.¹⁴

Because of the association between estrogens and cognitive functioning, it is theoretically possible that endocrine therapy for breast cancer may also have an effect on cognitive functioning. Although endocrine therapy is widely used among breast cancer patients, the potential effects on cognitive functioning have hardly been studied.

Clinical importance of a study into potential cognitive side effects of endocrine treatment

Evaluation of potential cognitive effects of endocrine treatments for breast cancer is relevant because intact cognitive functioning is considered to be an important aspect of quality of life.¹⁵ The impact of a decrease in cognitive functioning on a patient's quality of life might depend on, among others, the requirements of someone's professional and social situation relative to her cognitive capacities. As a consequence, this impact might vary from woman to woman. Nevertheless, possible declines in cognitive functioning are a source of concern for many people. A specific study on the effects of endocrine treatments on cognitive functioning will improve the understanding of possibly distinctive, cognitive effects of different endocrine treatments. Furthermore, attention needs to be paid to the experiences of patients with respect to this important quality of life facet, as well as to the roles of other factors, such as anxiety/depression, fatigue, and endocrine treatment-specific side effects, in cognitive functioning. The derived knowledge can be used to provide patients and health care professionals with evidence-based information and guidelines regarding cognitive functioning. Such information has been scarce up to now. In the future, the derived knowledge may also be used for the development of intervention techniques for cancer patients who suffer from cognitive complaints and/or cognitive dysfunction.

Neuropsychological substudy of the TEAM trial

In 2001, the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial started. The TEAM trial is an international, open-label, randomized study in postmenopausal hormone-sensitive breast cancer patients comparing the efficacy and safety of 5 years of adjuvant exemestane (25 mg/day) with 2.5 to 3 years of tamoxifen (20 mg/day) followed by 2 to 2.5 years of exemestane. This large international trial had national side studies regarding specific safety aspects, such as effects on bone health¹⁶ and blood lipids.¹⁷ The current thesis reports the results of the Dutch neuropsychological side study of the TEAM trial. This side study aimed to evaluate the effects of two endocrine treatments (the SERM

tamoxifen and the AI exemestane) on cognitive functioning in the context of a randomized design. Cognitive functioning was measured with a battery of neuropsychological tests, covering distinctive cognitive functions. The prospective character of the study and the inclusion of several self-reported measures of cognitive functioning and quality of life enabled us to investigate several additional relevant issues. Examples are the potential presence of cognitive dysfunction before the start of endocrine treatment and associations between self-reported cognitive functioning and cognitive test performance.

Outline of this thesis

Chapter 2 presents an overview of the current literature about possible influences of endocrine therapy for postmenopausal breast cancer on cognitive functions, such as memory, information processing speed and executive functioning. The first part of the review will provide an introduction to the influence of estrogens on cognitive functioning, with a focus on the effects detected in women during or after the menopausal transition. In the second part, the neuropsychological literature on the impact of endocrine therapy on cognitive functioning of breast cancer patients will be reviewed.

In **Chapters 3** and **4**, two studies with regard to cognitive functioning before the start of endocrine treatment are described. In the first study (**Chapter 3**) we examined the impact of four different definitions of cognitive impairment and two types of reference data (i.e., data from healthy postmenopausal women collected in the realm of the current study versus published normative data) on the prevalence of cognitive impairment. The second study (**Chapter 4**) aimed to identify medical and psychological predictors for cognitive performance of breast cancer patients before the start of adjuvant treatment, and to compare cognitive performance of breast cancer patients and healthy controls, adjusted for medical and psychological variables.

Chapter 5 describes the core study of this thesis, a prospective study investigating the effects of tamoxifen and exemestane on cognitive functioning of postmenopausal breast cancer patients who had not received chemotherapy. Breast cancer patients participating in the TEAM trial underwent neuropsychological examinations before the start of tamoxifen or exemestane treatment, and after one year of continuous treatment. A healthy control group consisting of friends and relatives of the patients underwent the same tests twice with an interval of one year. One of the advantages of including a control

group is the possibility to account for practice effects which are inherent to repeated neuropsychological testing. Because of the prospective nature of the study, we were able to adjust for the cognitive differences between the groups at the first cognitive assessment.

Chapter 6 describes a cross-sectional study investigating neuropsychological functioning in postmenopausal breast cancer patients receiving endocrine treatment after completion of chemotherapy. Participants were breast cancer patients, included in the TEAM trial, who were randomly allocated to tamoxifen or exemestane after completion of doxorubicin/cyclophosphamide (AC) chemotherapy. They underwent neuropsychological examinations on average 2 years after continuous tamoxifen or exemestane treatment. The study aimed to compare cognitive functioning of AC/tamoxifen users with that of AC/exemestane users, and to compare cognitive functioning of the combined patient group with that of healthy control women.

The study described in **Chapter 7** focused on self-reported cognitive functioning of breast cancer patients who used tamoxifen or exemestane. The prevalence of cognitive complaints and the self-reported frequency of cognitive failures, as well as associations between self-reported cognitive functioning, cognitive test performance, anxiety/depression, fatigue and menopausal complaints were evaluated.

The general discussion, **Chapter 8**, presents the aims and main conclusions of the studies. 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.

Reference List

- (1) Association of Comprehensive Cancer Centers. *Incidentie van invasieve tumoren naar geslacht en lokalisatie per incidentiejaar (1989-2007)*. 2010. http://www.ikcnet.nl/uploaded/docs/Landelijk/cijfers/incidentie%202007/A01_NL.xls. [accessed March 25, 2010].
- (2) van Nes JG, Seynaeve C, van de Velde CJ, Nortier JW. [Optimal adjuvant hormone therapy in postmenopausal women with hormone-sensitive mammary carcinoma: tamoxifen and the aromatase inhibitors anastrozole, exemestane and letrozole]. *Ned Tijdschr Geneeskd*. 2006;150:2863-2869.
- (3) Dowsett M, Cuzick J, Ingle J et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol*. 2010;28:509-518.
- (4) Perez EA. Safety profiles of tamoxifen and the aromatase inhibitors in adjuvant therapy of hormone-responsive early breast cancer. *Ann Oncol*. 2008;18(Supplement 8):viii26-viii35.
- (5) Schagen SB, Vardy J. Cognitive dysfunction in people with cancer. *Lancet Oncol*. 2007;8:852-853.
- (6) Sherwin BB. Estrogen and cognitive functioning in women. *Endocrine Reviews*. 2003;24:133-151.
- (7) Norbury R, Cutter WJ, Compton J et al. The neuroprotective effects of estrogen on the aging brain. *Exp Gerontol*. 2003;38:109-117.
- (8) Henderson VW. Estrogen-containing hormone therapy and Alzheimer's disease risk: understanding discrepant inferences from observational and experimental research. *Neuroscience*. 2006;138:1031-1039.
- (9) Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology*. 1992;17:485-495.
- (10) Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. *Psychoneuroendocrinology*. 1988;13:345-357.
- (11) Rocca WA, Bower JH, Maraganore DM et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. *Neurology*. 2007;69:1074-1083.
- (12) Shumaker SA, Legault C, Kuller L et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291:2947-2958.
- (13) Anderson GL, Limacher M, Assaf AR et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291:1701-1712.
- (14) MacLennan AH, Henderson VW, Paine BJ et al. Hormone therapy, timing of initiation, and cognition in women aged older than 60 years: the REMEMBER pilot study. *Menopause*. 2006;13:28-36.
- (15) Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365-376.
- (16) Hadji P, Ziller M, Kieback DG et al. The effect of exemestane or tamoxifen on markers of bone turnover: results of a German sub-study of the Tamoxifen Exemestane Adjuvant Multicentre (TEAM) trial. *Breast*. 2009;18:159-164.
- (17) Markopoulos C, Polychronis A, Dafni U et al. Lipid changes in breast cancer patients on exemestane treatment: final results of the TEAM Greek substudy. *Ann Oncol*. 2009;20:49-55.