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

Schilder, C.M.T.

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Chapter 3

The impact of different definitions and reference groups on the prevalence of cognitive impairment: a study in postmenopausal breast cancer patients before the start of adjuvant systemic therapy

Christina M Schilder, Caroline Seynaeve, Sabine C Linn, Willem Boogerd, Chad M Gundy, Louk V Beex, Frits S van Dam, Sanne B Schagen.
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Abstract

Objective: Several prospective studies into the effects of adjuvant systemic therapy on cognitive functioning suggest that a proportion of breast cancer patients show cognitive deficits already before the start of systemic therapy. Due to, among others, methodological inconsistency, studies report different rates of this pre-treatment cognitive impairment. We examined the impact of four different criteria of cognitive impairment and two types of reference groups (a study-specific healthy reference group versus published normative data) on the prevalence of cognitive impairment.

Methods: Two-hundred and five postmenopausal breast cancer patients underwent a battery of neuropsychological tests before the start of endocrine therapy, 124 healthy subjects underwent the same tests. Proportions of cognitive impaired patients were calculated for each of four criteria for cognitive impairment, using (1) study-specific healthy controls and (2) published norms of healthy controls as reference groups.

Results: 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 strictest to 36.6% for the less strict criterion, cognitive impairment relative to study-specific healthy controls, ranged from 13.7% to 45.4% for the same criteria.

Conclusion: This study highlights contrasting proportions of cognitive impairment by using different criteria for cognitive impairment and different reference groups. (Dis)advantages of methods using a criterion for cognitive impairment, and of the use of published norms versus a study-specific reference group are discussed.

Introduction

The development of effective adjuvant chemo- and endocrine therapy led, besides the results of screening, to a substantially increased survival of breast cancer patients. Therefore, more attention is actually paid to the late side effects of treatments that affect quality of life in breast cancer survivors, such as cognitive impairment. In the past years, a growing number of studies documented the presence of cognitive impairment in a subgroup of cancer patients treated with adjuvant systemic therapy. As most studies were cross-sectional with cognitive assessments performed months to years after chemotherapy, it was impossible to analyze individual changes in cognitive performance over time or to control for baseline differences between groups. Therefore, the use of a prospective study design with a baseline assessment before the start of adjuvant systemic therapy is currently thought imperative.[1]

One of the surprising findings in several prospective studies is that a subset of patients already shows cognitive deficits before the start of chemotherapy (see table 1 for an overview of the prospective studies which reported about cognitive functioning before the start of chemotherapy). The proportions of patients classified as 'cognitively impaired' at baseline vary from 11%[2] up to 35%.[3] The finding of cognitive impairment before treatment emphasizes the need to study the mechanisms that could explain this phenomenon. In the literature several mechanisms have been proposed for pre-treatment cognitive dysfunction, for example impact of anxiety and depression on cognitive functioning (although these relationships appeared to be typically absent in studies so far)[4] and negative effects of anesthesia and surgery undergone in the weeks before the baseline cognitive assessment.[5] Specific disease-related factors, such as increased levels of proinflammatory cytokines have also been proposed as possible cause for cognitive impairment in cancer patients before treatment.[6] Research in various neurodegenerative disorders, and in cancer patients receiving immunotherapy, has found associations between deregulation of cytokine activity and cognitive performance.[7,8]

Besides such subject-related matters, the extent to which pre-treatment cognitive impairment is observed might also be dependent on the methodology used to describe cognitive performance. For example, the results from analyses in which mean test scores of groups of patients/controls are compared can differ from analyses in which individual patients are classified as 'cognitively impaired' or 'intact' on the basis of a specific

definition. In the latter, different definitions for 'cognitive impairment' can lead to substantial differences in the observed prevalence of cognitive impairment.[9] Furthermore, when a large number of tests are used, a particular definition could lead to a higher estimated prevalence of cognitive impairment than when the same definition is applied to a smaller battery of tests. Another potential source of variation in the observed prevalence of cognitive impairment is the chosen reference group, namely whether published normative data or a healthy reference group, composed for the particular study is used.

The methodological issues mentioned above are well known and generally accepted in the neuropsychological literature. In research into other neurocognitive states that are characterized by relatively mild cognitive problems, like 'Mild Cognitive Impairment'[10], post-operative cognitive dysfunction[11] and HIV-associated neurocognitive disorders[12], these issues also get attention. In cognitive studies in cancer patients these specific factors are often not considered explicitly. For example, often no clear rationale is given for the choice of a particular criterion for cognitive impairment or for the use of a particular reference group. Furthermore, the impact of the choice for a particular criterion or particular reference group on the results and interpretation of cognitive data remains frequently not discussed.

The focus of this study is on methodological issues of the assessment of cognitive performance in cancer patients. We aimed to investigate the impact of different definitions for cognitive impairment and different reference groups (published norms versus our own study-specific healthy control group) on the observed prevalence of cognitive impairment before the start of adjuvant systemic therapy in breast cancer patients. The results of a more in-depth subject-matter analysis of cognitive performance of breast cancer patients before the start of adjuvant systemic therapy will be reported separately.

Table 1. Methods used to determine cognitive dysfunction prior to adjuvant systemic treatment in breast cancer patients

Authors	Compared to	Method	Result
Wefel et al, 2004[3]	Published norms	A patient was classified as cognitively impaired if she had multiple test scores of <-1.5 SD or 1 test score <-2SD below the normative mean. Patients completed 5-14 tests	35% of the patients were classified as cognitively impaired
Cimprich et al., 2005[13]	Published norms	Comparison of group mean scores with normative means	Mean test scores generally fell within the normal range for healthy adults
Fan et al., 2005[14]	Study-specific healthy controls	For each of six subtests, an interpretive algorithm was applied to generate a result of normal, borderline, mild, moderate or severe impairment. An overall classification of neurocognitive dysfunction was determined using another algorithm	16% of the patients and 5% of the controls had moderate-severe cognitive dysfunction (p.=.02)
Schagen et al., 2006[15]	Non-chemotherapy control group + Study-specific healthy controls	A patient was classified as cognitively impaired when she scored ≥2 SD's below the mean of the healthy group on at least 3 of 24 test indices. This definition yields a 'misclassification' rate of 10% in the healthy control group	Before treatment: 12.8% of FEC pts, 21.4% of CTC pts, 29.8% of non-chemotherapy pts and 10% of healthy controls were classified as cognitively impaired (not statistically significant different)
Hurria et al., 2006[2]	Published norms	A patient was classified as cognitively impaired when she score 2 SD's below the published normative data on at least 2 out of 12 test indices	11% of patients were classified as cognitively impaired.
Jenkins et al., 2006[16]	Non-chemo-therapy group + Study-specific healthy controls	Stepwise multiple regression using treatment group as a predictor, besides age, IQ, education, psychological distress and menopausal status	'Treatment group' did not significantly predict performance on any of 14 measures
Bender et al., 2006[17]	Endocrine therapy controls	Comparison of group means	No statistically significant difference between groups
Hermelink et al., 2007[18]	Published norms	Comparison of group means with normative means + individual classification (a patient was classified as cognitively impaired when she had ≥2 test scores (out of 12) in the lower 5% range	Group means were lower than normative means on 5 tests; 31% of the patients were classified as cognitively impaired
Ahles et al., 2008[7]	Study-specific healthy controls	A patient was classified as having 'lower than expected cognitive performance' if she scored ≥1.5 SD below the mean of the control group on ≥3 out of 9 domains or ≥2 SD below the mean on ≥2 domains.	0% of stage 0 patients and 22% of stage 1-3 patients were classified as having 'lower than expected cognitive performance'
Stewart et al. 2008 [19]	Endocrine therapy controls + published norms	Comparison of group mean scores with normative means	All mean test scores fell within the normal range relative to published norms

FEC = chemotherapy with 5-Fluorouracil, Epirubicin and Cyclophosphamide.
CTC = high dose chemotherapy with Cyclophosphamide, Thiotepa and Carboplatin, with bone marrow rescue.

Method

Participants and enrollment procedure

In the context of a prospective study on the impact of endocrine therapy on cognitive functioning, we conducted neuropsychological assessments in postmenopausal breast cancer patients after surgery, but before the start of any adjuvant systemic therapy. A group of healthy females of approximately the same age underwent the same neuropsychological testing.

Patients were female breast cancer patients participating in the Tamoxifen and Exemestane Adjuvant Multinational trial (TEAM trial; an international, open label, randomized study). The TEAM trial compares the efficacy and safety of 5 years of adjuvant exemestane (an aromatase inhibitor) with 2.5 years of tamoxifen (a selective estrogen receptor modulator) followed by 2.5 years of exemestane in postmenopausal women with early hormone sensitive breast cancer. Full in- and exclusion criteria of the Dutch TEAM trial are described elsewhere.[20] In short, patients had histologically/cytologically confirmed adenocarcinoma of the breast, had undergone surgery with a curative intent and had an estrogen receptor- and/or progesterone receptor-positive tumor. For this neuropsychological side study, only patients who were not scheduled to receive chemotherapy were eligible. Additional exclusion criteria were: Central Nervous System (CNS) disease, not being fluent in Dutch and signs of dementia according to a dementia screenings tool (7 minutes screen).[21] A central medical ethics committee and the local medical ethic committees of all participating hospitals approved the neuropsychological study. Enrollment of patients took place between October 2003 and January 2006. Patients were approached by their clinicians; the researchers carried out the informed consent procedure. The neuropsychological assessments took approximately 2.5 hours to complete. For each participant the administration of tests and questionnaires took place in the same order. A healthy control group consisted of female friends or family members of approximately the same age of the participating TEAM patients. We chose a healthy control group to minimize sociodemographic differences between the patients and controls. Inclusion criteria for controls were: postmenopausal status, no history of malignant disease or CNS disease, fluent in the Dutch language and no signs of dementia according to a dementia screenings tool (7 minutes screen).[21]

Assessment of neuropsychological performance

A comprehensive test battery was designed to assess a broad range of eight specific cognitive domains, comprising 18 test indices (see table 2). The choice for these eight domains was based on (1) earlier studies into the cognitive effects of chemotherapy which indicated that impairment was found in multiple cognitive domains and (2) literature-based hypotheses about the cognitive effects of estrogens.[22] The results with respect to baseline performance on these cognitive domains will be reported separately.

Besides the 18 outcome-variables, the Dutch Adult Reading Test[23] was used as a measure of pre-morbid verbal intelligence. Also, a dementia-screening tool was included to detect participants with signs of beginning dementia (7-minutes screen).[21] The tests were selected for reliability, validity, availability of published normative data and suitability for older age groups. All tests are widely used in clinical neuropsychological practice and the psychometric properties are well described.

Data-analysis

The Statistical Package for Social Sciences (SPSS) Windows 15.0 was used for statistical analyses. In case neuropsychological test scores were missing (approximately 0.7% of the total number of test scores), estimates on the base of age and IQ were imputed using an expectation-maximization (EM) algorithm implemented in SPSS. Patients and controls were then divided into 'cognitively intact' versus 'cognitively impaired' groups. In order to do so, we defined failure on an individual test as a score at least 2 SD's below the mean using (1) healthy controls and (2) published norms as a reference. This cut-off point is chosen as it is generally considered meaningful in clinical neuropsychological practice.[21,24] The distribution of cognitively impaired versus intact participants was described using four different, commonly used definitions, decreasing in strictness (failure on ≥4, ≥3, ≥2 and ≥1 test, respectively). For each definition and each reference group (published norms and our study-specific healthy control group), differences in proportions of cognitively impaired persons were tested by means of Chi^2 and logistic regression analyses. A *P*-value less than 0.05 was required for significance.

Table 2. Summary of cognitive test measures, outcome variables and origin of published norms

Cognitive domain	Cognitive tests	Outcome variable	Score range	Origin of norms	Adjusted for
Verbal memory	Rey auditory verbal learning test [25] (Dutch shortened version)	1. Total of 3 trials 2. Total for long delay trial	0-45 0-15	Data from a Dutch population-based study among 3107 participants aged 55-85 years [27]	Age Sex Education
	Visual Association Test[26]	3. Total of 2 trials	0-24	Dutch patients (n=540; age 16-62 years) with various neurological ailments	
Visual memory	Wechsler Memory Scale revised – visual memory [28] 1. Immediate recall 2. Delayed recall	4. Points awarded according to scoring criteria 5. Points awarded according to scoring criteria	0-41 0-41	American normative data from WMS manual	Age
Working memory	WAIS III Letter-number sequencing [29]	6. Total correct trials	0-21	Normative data of the Dutch Version of the WAIS-III	Age
Information processing speed	Stroop Card 1 [30]	7. Seconds to complete	0+	Stroop test: based on 585 persons aged 14-87 yrs from two population-based studies (n=330), healthy volunteers (n=65) and patients who appeared cognitive intact in clinical cognitive examination (n=190)	Age Sex Education
	Stroop Card 2 [30]	8. Seconds to complete	0+		
	Trailmaking A [31]	9. Seconds to complete	0+		
Mental Flexibility	Stroop Card 3 [30]	10. Seconds to complete	0+	Trailmaking test: based on 342 persons aged 17-87 yrs from a population -based study (n=78), healthy volunteers (n=66) and patients who appeared cognitive intact in clinical cognitive examination (n=198)	Age Sex Education
	Trailmaking B [31]	11. Seconds to complete	0+		
Reaction Times	Fepsy Reaction times: [32] 1. dominant hand 2. non-dominant hand	12. Mean msec/30 trials 13. Mean msec/30 trials	0+ 0+	Normative data from FePsy (1995). Based on 27 healthy controls aged 31-65+.	Age
Manual motor speed	Fepsy Finger tapping: [32] 1. dominant hand 2. non-dominant hand	14. Mean score of 5 trials of 10 seconds 15. Mean score of 5 trials of 10 seconds	0+ 0+	American normative data from Trahan et al. (1987). Based on 35 females aged 48-62 and 19 females aged 63-91.	Age Sex
Verbal fluency	Letter fluency (D,A,T)[33]	16. Total score of 3 letters/1 minute each	0+	Based on 200 healthy volunteers aged 17-89 years.	NART-IQ
	Category Fluency (Animals/professions) [34]	17. Total score 1 minute 18. Total score 1 minute	0+ 0+	Normative data from a Dutch population–based study among 1856 healthy persons aged 24-81 years.	Age, Sex Education

WAIS = Wechsler Adult Intelligence Scale; NART = National Adult Reading Test.

Results

Participant characteristics

Three hundred and thirty-one TEAM patients were eligible for the study in the period of enrollment. Eighty-five patients (26%) refused to participate because of lack of interest or too much burden, while 40 participants (12%) could not be included in the study, mainly due to logistic problems in the respective hospitals. Ultimately, 206 patients were tested (participation rate: 62%), whereby one patient was excluded from further analyses because of a score above the cut-off score of the dementia screenings test (7 minutes screen). The final study sample consisted of 205 patients. In the comparison group 124 healthy controls were included (none were excluded based on performance on the 7 minutes screen).

Table 3 shows the sociodemographic characteristics of the study sample. There were small, but statistically significant differences between the patient- and the control group for age, level of education and for estimated premorbid IQ. Therefore, subsequent analyses were, if appropriate, adjusted for age and IQ differences.

Table 3. Sociodemographic characteristics of the study subjects

	Patients (n=205)	**Controls (n=124)**	***P*-value**
Mean age, yrs (SD)	68.9 (7.4) range 50-84	66.5 (8.0) range 49-87	0.006
Marital status, % (n) [a]			
Married	61.0 (125)	59.7 (74)	0.82
Single	39.0 (80)	40.3 (50)	
Education, % (n) [b]			
Low	32.7 (67)	17.7 (22)	0.005
Middle	48.3 (99)	52.4 (65)	
High	19.0 (39)	29.8 (37)	
Premorbid IQ (SD) [c]	99.8 (19.5) range 56-140	105.5 (19.0) range 59-140	0.009

[a] Single = Widowed, divorced, separated, never married.
[b] Low: primary school, Middle: secondary school, High: Graduate school/University.
[c] Estimated with the National Adult Reading Test.

Neuropsychological test norms

For all tests, we selected the most appropriate normative data that were available in the Netherlands (see table 2 for the origin of the normative data). Criteria for selection were: based on cognitive intact, Dutch speaking controls; recently published or made available,

taking into account sex, age and/or education or IQ, and providing data from an elderly age cohort. For most tests, normative data met these requirements.

Prevalence of "cognitive impairment" relative to different definitions and different normative standards

The proportions of patients classified as 'cognitively impaired' were, for all four definitions, substantially higher when we compared them with our study-specific control group than when we compared them with published normative data (see table 4), but none of the differences remained statistically significant after adjustment for age and IQ.

The left part of table 4 shows, based on the scores of our own healthy controls, the proportions of patients and healthy controls classified as 'cognitively impaired' according to four different definitions, decreasing in strictness. As expected, the proportions 'cognitively impaired' patients and controls increased when the strictness of the definition decreased. When we determined the proportions of 'cognitively impaired' persons in the patient group and in our study-specific healthy control group on the base of published normative data (right part of table 4), we found that application of the two strictest definitions resulted in very low proportions of cognitively impaired persons in both the patient- and the control group (0.8% – 3.2%). Decreasing the strictness resulted, as expected, in higher proportions, but for none of the definitions statistically significant differences were observed between patients and healthy controls.

Table 4. Patients and controls classified as 'cognitively impaired' using different criteria and different normative standards

	Compared to our own control group				**Compared to normative data**		
No. of tests failed	Patients % (n)	Own controls % (n)	*P*	*P**	Patients % (n)	Own controls % (n)	*P*
≥4 tests failed	13.7 (28)	5.6 (7)	0.03	0.20	1 (2)	0.8 (1)	1.0
≥3 tests failed	17.6 (36)	8.1 (10)	0.02	0.21	2.4 (5)	3.2 (4)	0.73
≥2 tests failed	27.3 (56)	13.7 (17)	0.004	0.14	11.2 (23)	10.5 (13)	1.0
≥1 tests failed	45.4 (93)	33.1 (41)	0.03	0.70	36.6 (75)	31.5 (39)	0.40

P: *p*-value of Chi^2 test; *P*: p*-value of logistic regression with covariates age and IQ.

Discussion

The aim of this study was to demonstrate the impact of different definitions and different reference groups on the estimated prevalence of cognitive impairment before the start of adjuvant endocrine therapy in breast cancer patients. In cognitive studies with cancer patients many different definitions for cognitive impairment are used, often without a clear rationale. In addition, some studies made use of published norms [2,3,13,18,19] while other studies included a study-specific healthy reference group.[7,14-17,19] The impact of these methodological differences on the study results and interpretation is difficult to estimate and, as a consequence, the comparability of the studies is limited.

Our analyses showed that the prevalence of cognitive impairment varied greatly with the strictness of the definition, as expected (range from 13.7 % to 45.4% based on study-specific controls; range from 1% to 36.6% based on published norms). We also found that the estimated prevalence of cognitive impairment varied greatly as a function of the reference group used (study-specific healthy controls versus published data of healthy controls). For example, with cognitive impairment defined as failure on ≥2 tests, we found a prevalence of 27.3% when we used study-specific controls, versus 11.2% when we used published normative data.

With respect to definitions for cognitive impairment, a disadvantage of all methods using such definitions is that they are based on more or less arbitrary decisions, which can influence the results substantially. This applies for the cut-off point for failure on a single test and for the number of failed tests to classify a person as 'cognitively impaired'. Another drawback of methods that use definitions is that continuous data from multiple tests is reduced to only two categories ('cognitively unimpaired' versus 'cognitively impaired'). Categorizing continuous data leads to loss of information; therefore it might be more difficult to find small differences that have statistical and, potentially, clinical significance. The extent to which methods using definitions and methods comparing mean test scores between groups will produce different results depends on, among others, group sizes and the distribution of test scores within the groups.

With respect to reference groups, an advantage of the use of a study-specific reference group above published norms is the possibility to evaluate the impact of a particular criterion on the calculated prevalence of 'cognitive impairment' in the reference group

and to compare the calculated proportions in patients and controls. This provides the possibility to prove the particular criterion. If only published norms are used, such a check is not possible, leaving uncertainty about the accurateness of the chosen criterion and, subsequently, the reported proportion of 'cognitively impaired' patients. Another advantage of a study-specific reference group above published norms is that the same tests are applied on both patients and controls. Published normative data of each test originate from different normative samples of possibly diverse quality, reducing the possibilities to combine different tests to, for example, cognitive domains or to compare different test results with each other. However, study-specific reference groups are not without problems too. For example, in study-specific reference groups consisting of family and friends (as in the current study), selection bias is easily introduced because patients might invite persons who they consider at ease with cognitive testing and/or have a higher mean IQ than the patients themselves. Additionally, it is often not easy to compose a study-specific reference group of a sufficient size. In such cases, normative data derived from a large age- and IQ stratified sample might be preferred above a small study-specific reference group.

Our data showed, in the comparison of the patients with our own controls, that the proportions of 'cognitively impaired' persons differ significantly before adjustment for age and IQ, but that these differences are not longer significant after adjustment for these covariates. This indicates that small differences in age an IQ between the groups have a substantial impact on the test results. Because age and IQ are well known predictors for cognitive performance[24] and are probably even more prominent in older age groups, our data stress the importance of taking these covariates into account sufficiently. When a study-specific reference group is used, careful matching on these variables is important. When published norms are used, large normative samples in which elderly subgroups are represented sufficiently are imperative.

The strength of this study is that the size of both the patient- and the healthy control group is high compared to other study samples in this research field. A limitation of our study might be the suboptimal quality of the published norms for several tests that we used, possibly having biased the results. The development of normative data is an expensive and time-consuming matter that often has less priority than it deserves. This is especially a problem in small countries or small language areas, such as the Netherlands.

Although the quality of published norms is probably better in larger countries, shortcomings in the quality of the published normative data seem to be universal[21] and can influence the results to a large extent. Another limitation is the non-perfect match with respect to age and IQ between our patients and healthy controls, making statistical adjustment for these differences necessary.

In conclusion, the estimated prevalence of cognitive impairment in a particular patient group is highly dependent on the used definition for cognitive impairment and the reference group to which patients are compared. As a consequence, the scope of the problem of cognitive impairment before the start of adjuvant systemic treatment for breast cancer is not yet sufficiently clear. In some studies conducted so far the prevalence of cognitive impairment is probably overestimated due to the use of a relatively 'weak' criterion combined with the lack of a study-specific reference group, as a result of which the criterion could not be proved.[3,18]

Our data stress the need for consensus on the measures and statistical methods to study cognitive impairment both before as during/after adjuvant systemic therapy. Considering the methods used in neuropsychological studies in other patient groups that are characterized by mild cognitive impairment might be helpful in reaching this consensus. In order to find the best methods to evaluate cognitive impairment associated with cancer and cancer treatments, an international group of researchers started a Task Force in order to stimulate standardization and improvement of research methods.[35]

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