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REHABILITATION OF THERAPY-RELATED COGNITIVE DEFICITS IN PATIENTS WITH BREAST CANCER

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Abstract

Among various side effects of adjuvant chemotherapy neuropsychological deficits have been described within the last two decades. A literature review shows that especially breast cancer women after adjuvant chemotherapy are suffering from these deficits. Against this background the need for special rehabilitation programms has been discussed to help the patients to cope with this sequelae, but there are only few attempts for special neuropsychological training programms for cancer patient. In the study presented we compared two types of neuropsychological interventions in a rehab setting against a control group with no specific training in a total of 96 female in-patients undergoing inpatient oncological rehabilitation. Most results of a comprehensive neuropsychological test battery improved significantly during the patients' oncological rehabilitation in all three groups, whereas we could not identify a specific intervention effect neither between the two intervention groups nor between the treatment and control groups. In terms of the follow-up examination we found that clinically relevant neuropsychological deficits were still evident 6 months later in a small subgroup of patients.

Resumen

Los déficits neuropsicológicos se han descrito en las últimas dos décadas entre varios de los efectos secundarios de la quimioterapia adyuvante. Una revisión de la literatura muestra especialmente que las mujeres con cáncer de mama después de la quimioterapia adyuvante sufren de este déficit. En este contexto se ha discutido la necesidad de programas de rehabilitación especiales para ayudar a las pacientes a hacer frente a estas secuelas, pero hay sólo unos pocos intentos de programas de entrenamiento neuropsicológico para pacientes con cáncer. En el presente estudio se compararon dos tipos de intervenciones neuropsicológicas en un centro de rehabilitación con un grupo control sin entrenamiento específico, con un total de 96 mujeres hospitalizadas realizando rehabilitación oncológica. La mayoría de los resultados de una batería neuropsicológica compresiva mejoraban significativamente durante la rehabilitación oncológica de las pacientes en los tres grupos, mientras que no se pudo identificar un efecto de la intervención específica ni entre los dos grupos de intervención, ni entre los grupos tratamiento y control. En cuanto a los exámenes de seguimiento se encontró que los déficits neuropsicológicos

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Key words: Breast cancer, neuropsychological rehabilitation, cognitive deficits, side effects of chemotherapy, late effects of treatment.

clínicamente relevantes seguían siendo evidentes seis meses más tarde en un pequeño subgrupo de pacientes.

Palabras clave: Cáncer de mama, rehabilitación neuropsicológica, déficits cognitivos, efectos secundarios de la quimioterapia, efectos tardíos de los tratamientos.

INTRODUCTION

The aim of oncological rehabilitation is to identify physical, psychological, and social deficits, and to treat them via specific interventions[1]. A number of papers have been published recently focussing on cognitive deficits following CHT for breast cancer[2-9]. Yet they are difficult to compare due to major differences in study design, cohort make-up (i.e., age, CHT protocol, additional adjuvant therapies), the use of various neuropsychological test procedures, and the criteria for classifying neuropsychological deficits[10].

There is considerable agreement that cognitive deficits may be relevant, yet little consensus concerning the prevalence rates. However, there is general agreement that deficits are affecting the speed of information processing, attention, learning and memory, as well as "executive functions" (especially planning and effective performance of actions)[10,-13]. As one important result among some studies the correlation between neuropsychological test results and the patients' own appraisal of the deficits in their mental capability are low [3,5,14,5].

Most of the studies had a cross-section design; few were prospective in terms of how deficits change over the long term following the conclusion of CHT[4,7,8]; only one trial had included tests administered prior to the start of CHT[7] and revealed cognitive deficits in about a third of the patients at that point. While Wefel et al.[7] observed an increase in cognitive deficits immediately after the conclusion of CHT, the patients' test results one year later closely matched their scores at baseline. Still, most of the existing studies indicate that a subgroup of patients may present signs of cognitive deficits even long-term following adjuvant CHT.

There is little specific information on potential risk factors in the literature so far. Scherwath et al.[9] assigned a particular role to methotrexate in the context of chemotherapy according to the CMF-protocol (cyclophosphamide, methotrexate, 5-fluorouracil); investigations on the effects of adjuvant anti-hormonal therapy (AHT) for breast cancer (without concurrent CHT) also indicate the possibility of cognitive deficits[15,16,17]. Ahles & Saykin[11] discuss various theoretical models, yet there is no empirical proof justifying those approaches yet.

For the most part there is increasing agreement that cognitive deficits should be regarded as a potential consequence of adjuvant therapy for breast cancer. The descriptions of long-term survivors also reveal that cognitive deficits can substantially impair functional capabilities in everyday life[18].

Although leading experts in the field have been recommending the development and evaluation of targeted neuropsychological therapy strategies[11,13,19], only few studies have been accomplished on the subject so far. Clinical neuropsychologists have been developed a broad spectrum of

effective approaches for treating cognitive deficits as a consequence of neurological diseases and traumatic brain injury[20,21]. Among those approaches there is a basic distinction between "restitutive" approaches such as functional training and "compensatory" strategies. The goal of functional training is to improve specific performance shortcomings directly, whereby compensatory strategies attempt to compensate on an everyday basis for the permanent loss of skills by capitalizing on still-intact cognitive functions, or via targeted behavioral strategies[20]. While it is recognized that attentional skills can be improved by specific training, there is still no proof of specific functional improvement in memory, which is why the focus of neuropsychological therapy in that area lies in developing compensatory strategies[20,21].

Ferguson et al.[22] were the first to publish encouraging data from a cognitive training program for breast cancer patients (Memory and Attention Adaption Training MAAT). The program concentrated on compensatory strategies for improving everyday skills and relaxation techniques within the framework of four individual meetings and three interspersed telephone consultations. They demonstrated positive effects on attention, memory, and executive functions in an initial evaluation of 29 breast cancer patients whose CHT had been completed at least three years earlier. Moreover, they reported positive feedback from the patients regarding improvements in everyday mental skills.

PATIENTS AND METHODS

Against this theoretical background, it was the aim of our study to implement a cognitive therapy approach in the rehabilitation of breast cancer patients following adjuvant CHT and to evaluate their effects. The study was conducted at the rehabilitation unit of the Tumor Biology Center, Freiburg Germany. The patients in our study were participating in an in-patient rehabilitation programm following oncological therapy immediately after the end of the adjuvant therapy for a regular stay of three weeks. The rehabilitation program includes medical diagnostics and treatment, physical and sport therapy, psychosocial treatment and other interventions (e.g. nutrition therapy, art therapy) in order to improve disease- and treatment-related deficits in functional status and quality of life[23]. We developed two specific neuropsychological treatment strategies based on existing clinical neuropsychological approaches. The focus of both interventions was on improving functional attention and memory deficits which, according to the current literature, constitute the main potential problem areas for breast cancer patients.

The Neuropsychological Training Group (NPT), with a maximum of 8 participants, was led by a specialised occupational therapist who carried out a broad spectrum of activities concerned with attention and memory in everyday life. This type of training was focusing more real-life situation and was aimed to convey compensatory strategies that patients could apply directly in everyday activities. The training program has been collated in a manual comprising 15 units.

The second intervention was an individualized, computer-based training (PC) under continuous therapeutic supervision. We used training software from different suppliers and assigned tasks addressing specific dimensions of attention and memory according to the parameters of our neuropsychological test battery (see Table 1). The training was continuously adapted to suit the capabilities and training progress of the individual patient. Both interventions took part in four one-hour training sessions per week during their stay as in-patients.

The research questions were:

1) Do the both intervention groups (NPT and PC) significantly improve the neuropsychological test parameters or/ and the self-appraisal scales (see Table 1) compared with the control group (CG) receiving no specific cognitive training.

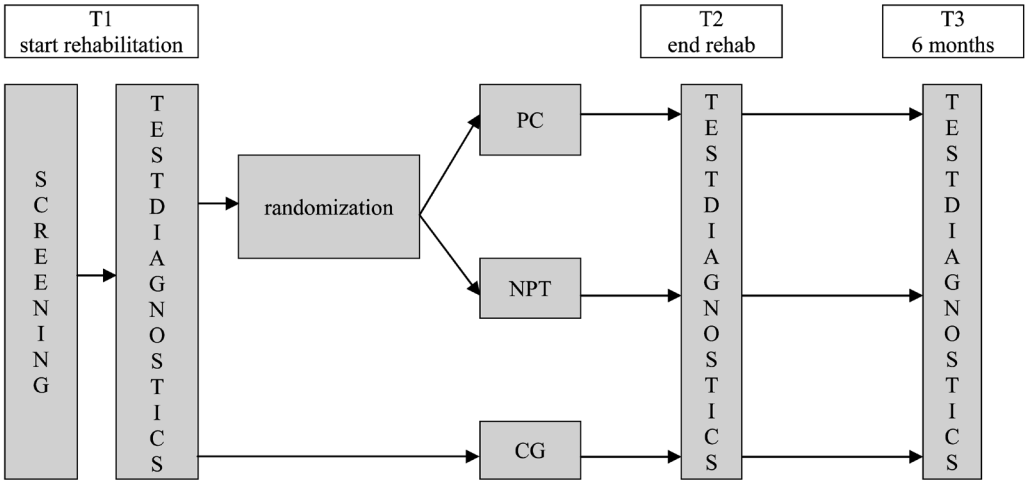
2) Are there any differences for the both neuropsychological interventions in terms of the neuropsychological test parameter and the self-appraisal of cognitive functioning in everyday life.

Measurements were taken upon admission to the rehabilitation unit (T1), at the end of rehabilitation (T2), and 6 months later on an out-patient basis (T3). Medical and sociodemographic data were acquired from the hospital's documentation system.

All participants were recruited consecutively between September 2002 and January 2004. They had undergone adjuvant CHT for stage I or II breast cancer. Exclusion criteria were: age over 64 years, previous history of cancer, history of psychiatric or neurological symptoms likely to lead to cognitive deficits, current use of psychoactive medication, and insufficient command of the German language. The study was approved by the Ethics Committee of the medical faculty at the University of Freiburg. Patients were randomly assigned to the training groups. As randomization to non-treatment during the in-patient rehabilitation program was not feasible in terms of obtaining the patients' acceptance, we recruited the CG over a "time-out" phase while we were offering no training. All participants provided written informed consent. Figure 1 shows the study design.

To identify patients with cognitive deficits requiring specific treatment, we used three sub-tests of the computerized "Test Battery for Attentional Performance TAP"[24], which had proved in an earlier study to be particularly sensitive in detecting cognitive dysfunction in cancer patients[25]. We chose five central measures ("Alertness": reaction times with and without warning signal, "Reaction Change": reaction time and errors, "Divided Attention": sum of errors and omissions) and defined the criterion for training requirement according to earlier neuropsychological intervention studies[26] as results within the lowest quartile of the norm sample in at least two of the five parameters.

Figure 1. **Study design**



PC: PC training; NPT: neuropsychological group therapy; CG: control group

Table 1. **Neuropsychological measures and questionnaires**

Test	Parameters	Dimensions
TAP: Alertness	RT with / without warning signal	basic information processing speed
TAP: Reaction Change	RT; false reactions	mental flexibility
TAP: Divided Attention	RT; sum of omissions and false reactions	divided attention
TAP: Go/NoGo	RT; false reactions	selective attention
TAP: Sustained Attention	omissions; false reactions	sustained attention
RBMT: Story	immediate and delayed reproduction	verbal-semantic memory
WMS-R: Digit Span	digit span forwards / backwards	short-term memory; working memory
LGT-3	city map; objects	figurative and spatial memory
Questionnaires	**Parameters**	
QLQ-C30: EORTC Quality of Life Questionnaire	Functional scales: Physical; Role; Cognitive; Emotional; Social; Global Health Symptom scales: Fatigue; Nausea & Vomiting; Pain; Dyspnoea; Insomnia; Appetite Loss; Constipation; Diarrhoea; Financial Impact	
MFI: Multidimensional Fatigue Inventory	Scales: General F.; Physical F.; Reduced Activity; Reduced Motivation; Mental F.	
HADS: Hospital Anxiety and Depression Scale	Scales: Anxiety; Depression	
FEDA: Questionnaire of Self-Perceived Deficits in Attention	Scales: Distractibility and Retardation in Mental Tasks; Fatigue and Retardation in Activities of Daily Living; Reduced Drive	

RT: mean reaction time; TAP: Testbatterie zur Aufmerksamkeitsprüfung ("Test Battery for Attentional Performance") (Zimmermann & Fimm[28]); RBMT: Rivermead Behavioral Memory Test (Wilson et al.[29]); WMS: Wechsler Memory Scale-R (Wechsler[30]); LGT-3: Lern- und Gedächtnistest ("Learning and Memory-Test") (Bäumler[31]); QLQ-C30: EORTC Quality of Life Questionnaire QLQ-C30 (Aaronson et al.[32]); MFI: Multidimensional Fatigue Inventory (Smets et al.[33]); HADS: Hospital Anxiety and Depression Scale (Herrmann et al.[34]); FEDA: Fragebogen erlebter Defizite der Aufmerksamkeit ("Questionnaire of Self-Perceived Deficits in Attention") (Zimmermann et al.[24]); Sturm[27]).

Patients fulfilling our inclusion criterion were asked to participate in the study. All study participants took a battery of standardized and validated neuropsychological tests for attention and memory. Health-related quality of life, fatigue and emotional status were evaluated using different questionnaires (see Table 1). Three questionnaire subscales (EORTC "Cognitive Functioning"; MFI "Mental Fatigue"; FEDA "Distractibility and Retardation in Mental Tasks") specifically measured the patients' self-appraisals of their everyday cognitive performance.

The EORTC scale consists of two items that very generally address the degree of deficit in attention and memory in everyday life, with four possible answers ranging from "not at all" to "very". The MFI scale, however, has four items concentrating exclusively on attention, with scores ranging between 1 and 5. We also administered the FEDA[24,26] to specifically evaluate attention deficits – it is a normed testing instrument used primarily in German-speaking Europe in neurological rehabilitation. The "Distractibility and Retardation in Mental Tasks" scale contains 11 items addressing

attention problems in concrete everyday situations; the five possible responses range from "very often" to "never". Since the correlations between neuropsychological functional level, self-appraisal and potential moderating variables are not the main focus of this paper, the questionnaires are presented in their entirety only for purposes of completeness. We are working on a manuscript addressing that specific topic.

The Statistical Package for Social Sciences (SPSS; Windows 12.0 software) was used for statistical analyses. As statistical procedure differences were tested using the χ^2-test for contingency and the Student's t-test. We used Pearson's r as correlation coefficient for normally distributed and Spearman's rho for not normally-distributed variables. Intervention effects were analyzed in a mixed model by means of multivariate analysis of variance (MANOVA). We adjusted the α-level for multiple testing according to Bonferroni from 0.05 to 0.0026.

A total of 335 women with breast cancer fulfilling our inclusion criteria were admitted as in-patients during the recruitment period (from September 2002 to January 2004). Based on the criteria for eligibility and after drop-outs due to various reasons we were able to include 96 patients with complete data at T1 and T2. The reasons for drop outs were lack of interest in the training program or in the test examinations. Only few patients dropped out of the study due to interim relapse of disease and discharge from rehabilitation. N=90 patients could also be assessed at the third measurement point. Reasons for drop-outs between T2 and T3 were recurrent tumor activity (N = 3), lack of motivation (N = 1), and loss due to organizational factors (N = 2). The distribution on the three intervention groups was as follows (numbers of patients also assessed at T3 in brackets): NPT: N = 33(33); PC: N = 34(32); CG: N = 29(25).

Table 2. **Sociodemographical and medical data**

			n	%
Age		**Professional Training**		
Mean (SD)	**49.19** (7.71)	Apprenticeship	**54**	56.3%
Range	32-64	Polytechnic	**19**	19.8%
		University	**16**	16.7%
		Other	**4**	4.2%
		None	**3**	3.1%
Time since first diagnosis		**Chemotherapy**		
Mean (SD)	**9.01** (3.39)	CMF	**13**	13.5%
Range	3 - 24	CMF + Anthracyclines	**7**	7.3%
		Anthracyclines	**47**	49.0%
		Anthracyclines + Taxanes	**29**	30.2%
Time since last treatment				
Mean (SD)	**2.06** (2.78)	**Antihormonal Therapy**	**68**	70.8%
Range	0 - 15	**Radiotherapy**	**86**	89.6%

CMF: cyclophosphamide, methotrexate, 5-fluorouracil; **Anthracyclines**: epirubicin or doxorubicin (in combination with cyclophosphamide); **Taxanes**: docetaxel or paclitaxel

RESULTS

Description of the sample

The average age in our sample was 49.19 (with a standard deviation [SD] of 7.71) years (Table 2). The level of education and professional training was above average: 16.7% (N = 16) of the sample had a university degree; only 3.1% (N = 3) were not professionally trained. The mean time since first diagnosis was 9.01 (3.39) months; time since conclusion of therapy (excepting AHT) was on average 2.06 (2.78) months. The CHT protocols our patients received reflect current clinical standards in treating breast cancer; the use of anthracyclines (docetaxel or paclitaxel) dominates. The vast majority of our patients underwent post-operative localized adjuvant radiation, and 70.8% (N = 68) were on AHT.

Neuropsychological test results at T1

We selected 16 neuropsychological test scores for statistical analyses. Data at T1 are presented with T-values as benchmarks as far as possible. Exact T-values are missing for the TAP error indices (false reactions; omissions) and RBMT "Story". Only percent rank norms are available for WMS "Digit Span". To assess the frequency of clinically relevant deficits in the different

Table 3. **Neuropsychological test results at T1 (n = 96)**

Test	RS	SD (RS)	T	SD (T)	Deficits	
					N	%
ALTO	289.47	55.13	40.73	7.21	14	14.6%
ALPH	274.95	52.28	40.81	7.08	15	15.6%
RCRT	932.95	255.80	45.33	7.92	8	8.3%
RCFR	2.93	3.18			8	8.3%
DART	711.26	79.96	43.03	8.89	18	18.8%
DAER	4.15	3.42			8	8.3%
GNRT	416.42	56.98	49.69	7.06	3	3.1%
GNFR	.75	1.15			1	1.0%
SAOM	11.88	7.37			47	49.0%
SAFR	7.17	8.93			19	19.8%
RBIM	9.48	3.18			30	31.1%
RBDL	8.45	3.31			33	34.4%
DSFW	8.07	1.88	*54.93**	*29.77**	4	4.2%
DSBW	7.58	1.92	*60.26**	*28.28**	3	3.1%
PLAN	14.64	4.63	43.53	8.17	15	15.6%
OBJC	9.60	2.49	50.47	9.06	3	3.1%

ALTO: Alertness tonic (without warning signal); **ALPH**: Alertness phasic (with warning signal); **RCRT**: Reaction Change, reaction time; **RCFR**: Reaction Change, false reactions; **DART**: Divided Attention, reaction time**; DAER**: Divided Attention, sum of false reactions and omissions; **GNRT**: Go/NoGo, reaction time; **GNFR**: Go/NoGo, false reactions; **SAOM**: Sustained Attention, omissions; **SAFR**: Sustained Attention, false reactions; **RBIM**: RBMT "Story" immediately; **RBDL**: RBMT "Story" delayed; **DSFW**: Digit Span forward; **DSBW**: Digit Span backward; **PLAN**: LGT-3 "City Plan"; **OBJC**: LGT-3 "Objects"; **RS**: raw score; **SD**: standard deviation; **T**: T-value * normed in percentiles.

parameters, we applied a criterion used in other studies[7] and defined results of at least 1.5 SD below the mean of age-adjusted norm data (corresponding to percent rank 6.7) as impaired. Since we noted no significant differences among the three groups, we have consolidated the results from the entire study group to facilitate clarity. Highest deficit rates were obtained from TAP "Working Memory and Sustained Attention" and from RBMT "Story", followed by both TAP "Alertness" parameters, reaction speed of TAP "Divided Attention" and the LGT-3-subtest "City Plan". 87.5% (N = 84) of our study patients scored in at least one neuropsychological parameter in the impaired range, for 56.2% (N = 54) this was the case in two or more parameters.

Multivariate analysis of the effects of training

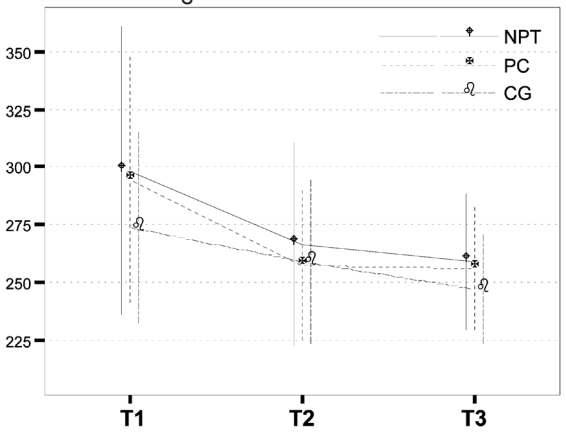
Both intervention groups received on average 11.88 (SD = 2.42) training sessions per patient, with only a minimal and statistically not significant difference (p = .225) between PC training (12.24; SD = 2.56) and the NPT group (11.52; SD = 2.24).

As the various parameters yielded very similar patterns, we illustrate the results from one attention and one memory test as well as one of the self-appraisal scales.

In TAP "Tonic Alertness" (without warning signal) we observed a clear improvement in performance (reduced reaction times) in all 3 groups between T1 and T2. The time effect was significant in that interval, while we noted no interaction effect between time and group (and thus no specific intervention effect). The differences between the CG and two intervention groups were not significant due to considerably great intragroup variances (the error bars indicate the range of one SD around the mean). Between T2 and T3 the curves flattened out quite obviously, we observed no time or interaction effect there either.

In RBMT "Story" (delayed recall), we also observed a significant time effect between T1 and T2 (higher scores indicate more correctly reproduced text components); the interaction effect failed to meet the adjusted α-level, although both RBMT parameters (immediate and delayed recall) revealed a concordant tendency: the NPT group (which had the lowest baseline scores) improved much more than did the CG. While the CG's performance continued to improve between T2 and T3, both intervention groups performed gradually worse at the last measurement

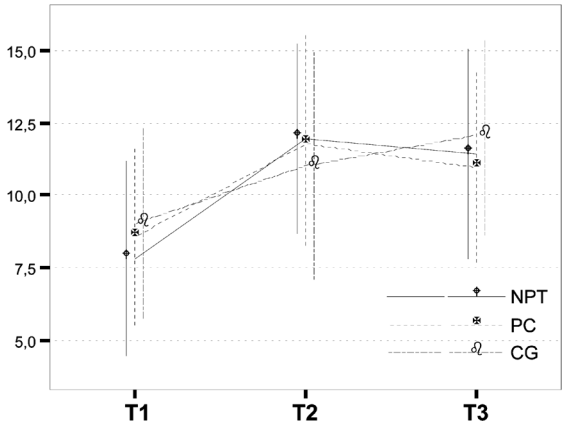
Figure 2. **Alertness without warning signal: reaction time**



MANOVA T1, T2, T3		df	F	p
Time	T1 - T2	1	29.283	**.000**
	T2 - T3	1	2.949	.090
Group	T1 - T2	2	1.339	.267
	T2 - T3	2	1.461	.238
Time * Group	T1 - T2	2	1.675	.193
	T2 - T3	2	.247	.781

N=95/89

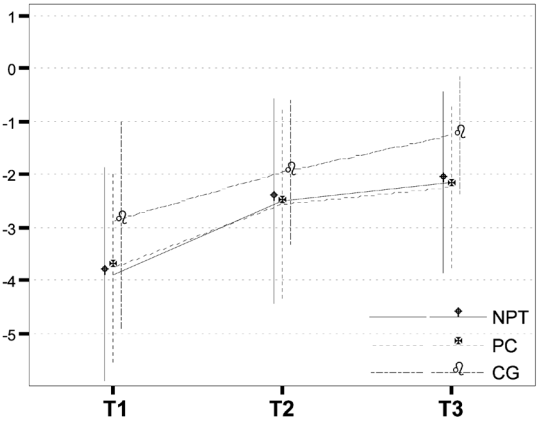
Figure 3. **RBMT Story: delayed recall**



MANOVA T1, T2, T3		df	F	p
Time	T1 - T2	1	119.531	**.000**
	T2 - T3	1	.424	.516
Group	T1 - T2	2	.076	.927
	T2 - T3	2	.122	.885
Time * Group	T1 - T2	2	4.870	.010
	T2 - T3	2	1.855	.163

N=96/90

Figure 4. **EORTC Cognitive Functioning**



MANOVA T1, T2, T3		df	F	p
Time	T1 - T2	1	51.042	**.000**
	T2 - T3	1	7.170	.009
Group	T1 - T2	2	1.936	.150
	T2 - T3	2	2.908	.060
Time * Group	T1 - T2	2	.649	.525
	T2 - T3	2	.156	.855

N=96/89

point. The three groups' results at T3 were very similar overall.

The EORTC-scale "Cognitive Functioning" showed general improvement between T1 and T2 (higher values indicate higher functional levels); variance analysis demonstrated a significant time effect; the improvement trend became weaker between T2 and T3 and failed to meet the adjusted level of significance. Again we detected no statistically significant group effects or interaction effects between time and group. Similar data were obtained from the other two self-appraisal scales (data not shown).

In general, we observed significant improvement in performance between T1 and T2 in 11 of the 16 neuropsychological parameters. There were no significant time effects in TAP "Go/NoGo" (reaction time), in either parameter of WMS "Digit Span", nor in the two LGT subtests. None of the neuropsychological parameters revealed either a significant group or interaction effect at both time intervals. The improvement trend became weaker between T2 and T3; we detected a significant time effect in only 6 of the 16 neuropsychological parameters. That was

the case in 4 of the 5 parameters that had shown no significant time effect between T1 and T2 (the exception: WMS "Digit Span forward").

6-month follow up at T3

Following our criterion of 1.5 SD under the mean of age-adjusted norm data at T3, we observed that 44.4% (N = 40) of our sample still displayed at least one deficitary result, 21.1% (N = 19) scored in two or more of the 16 neuropsychological parameters in the impaired range. We view the latter group as still cognitively impaired in a clinically-relevant sense. Although we identified an obvious general trend toward improvement in neuropsychological results, a subgroup of patients did remain that is still suffering from clinically-relevant cognitive deficits an average of one year after the end of cancer therapy. Again, TAP "Working Memory and Sustained Attention" and RBMT "Story" revealed the highest deficit rates. We attempted to identify predictors for neuropsychological deficits at T3 using various analyses (i.e., multiple regression analysis, cluster analysis). Medical and sociodemographic variables revealed no predictive value whatsoever; that was also the case for CHT according to CMF-protocol and adjuvant AHT (which had proven to be predictors for cognitive deficits at T1). The only significant parameter was the degree of neuropsychological deficits at T1, that is, the poorer a patient's performance was at baseline, the higher the risk that she would be classified as having deficits at T3.

We used reference data from the German general population for the EORTC-scale "Cognitive Functioning" for comparison with our sample. By applying the same criterion of 1.5 SD under the mean of age-adjusted norm data, we found that about 36% (N = 32) of our patients judged their everyday cognitive abilities to be below average.

Feedback from the training groups

We asked the patients at T2 for their opinion on the interventions. Table 5 illustrates how helpful they found the information we had provided on cognitive deficits after CHT and the personal counselling they had received concerning their test results. We also asked them at T2 and T3 how useful they found the training to have been. The feedback was overwhelmingly positive - the vast majority (92.3%) judged the information to be "fairly" or "very helpful", only 7.7% found it not so. We received the same positive feedback (93.8% "fairly helpful" or "very helpful") on the test-results counselling, which only 6.2% found not particularly helpful. Most found the training helpful; that appraisal was considerably better at T3 than that made immediately at the end

Table 4. **Training Feedback (participants NPT/PC: N = 67 [T2] / 65 [T3])**

Question	--		-		+		++	
Information*	**1**	1.5%	**4**	6.2%	**32**	49.2%	**28**	43.1%
Personal counselling*	**-**	-	**4**	6.2%	**23**	35.4%	**38**	58.5%
Usefulness of training T2**	**2**	3.0%	**10**	14.9%	**37**	55.2%	**18**	26.9%
Usefulness of training T3**	**-**	-	**2**	3.1%	**21**	32.3%	**42**	64.6%

* -- "not helpful at all"; - "not particularly helpful"; + "fairly helpful"; ++ "very helpful"

** -- "minimal"; - "quite low"; + "rather useful"; ++ "very useful"

of the training program. While 26.9% of the patients found the training groups to be "very helpful" at T2, 64.6% did so at T3; the low scores (usefulness rated as quite "low" or "minimal") fell from 17.9% at T1 to 3.1% at T3. There were no differences in this regard between the 2 intervention groups (data not shown). We believe these results and our patients' impressive motivation to clearly illustrate the importance of this issue and the subjective usefulness of such interventions for breast cancer patients after adjuvant CHT.

DISCUSSION

Although neurocognitive deficits after adjuvant chemotherapy have been described and investigated in many studies, there is a lack of knowledge in specific neuropsychological training programms in cancer rehabilitation. Therefore this is one of the first studies to systematically investigate the effects of specific neuropsychological rehabilitation strategies in breast cancer patients shortly after adjuvant therapy has been finished. Based on a randomized trial we aimed also to evaluate the feasibility of such a program in the context of in-patient cancer rehabilitation.

According to our criteria of neuropsychological impairment, we observed that 47.1% of the patients presented signs of possible cognitive deficits and the need for training. In line with the research literature our differentiated analyses of the neuropsychological test results revealed deficits especially in sustained attention, verbal-semantic memory, alertness (basic information processing speed), and divided attention; 87.5% of our study participants presented signs of clinically-relevant deficits in at least 1 of the 16 parameters we examined, and 56.2% did so in 2 or more.

We observed significant improvement in performance in most of the neuropsychological parameters during in-patient rehabilitation in all three study groups. Since the control group (without specific training) improved in the same manner as the PC and NPT training groups, we could not demonstrate any specific intervention effects.

There may be several factors leading to this general improvement trend. First of all, there may be an overall spontaneous remission starting soon after the end of adjuvant therapy – in terms of both cognitive performance and physical condition (we also observed solid physical improvement during in-patient rehabilitation; symptomatic complaints such as fatigue were considerably reduced). Furthermore, there may be an unspecific effect of the in-patient rehabilitation programm itself on cognitive skills, as it includes manifold physical, intellectual, and emotional stimulation. Finally, longitudinal neuropsychological investigations requiring the same or very similar tasks of the patients always reflect the "danger"of practice effects being behind demonstrations of improvement.

To monitor any "unspecific effects" of in-patient rehabilitation, one would have to include a control group of patients not receiving such rehabilitation. Identifying training effects within the context of repeated neuropsychological tests is a complex problem – besides choosing instruments less susceptible to such effects (i.e., by using tests with parallel versions of equal difficulty), it is worth considering an additional preceding baseline testing as well. The intervention phase would not start until the second test, thus minimizing most of the practice effects, which are generally most pronounced between the first and second testing. Another alternative would be to include a healthy control group of similar age and education. The recently-established „International Cognition and Cancer Task Force" is working on setting up

guidelines so that future research activities can be better coordinated and their results more readily compared[35].

Another possible explanation for our having failed to detect any significant intervention effects has to do with our inclusion criterion, which included patients presenting minor signs of neurocognitive deficits. Our cohort may well have included women whose capabilities were not at all or were only minimally impaired by CHT - meaning they would fail to demonstrate any substantial improvement after training.

In the period following in-patient rehabilitation, for the most neuropsychological parameters the improvement curves clearly flattened out. In that case, one must remember that that interval encompassed six months and lasted thus much longer than the in-patient rehabilitation. In a few parameters, especially the more complex memory tasks, we did not observe significant improvement until the T2-T3 interval. Perhaps these skills improve more slowly than "basic" attentional functions. The examination of improvement in various neuropsychological parameters over time would be an ideal subject for future investigations.

We did observe a strong general trend toward improvement in the neuropsychological test scores, yet our data also reveal a subgroup of patients showing clinically-relevant cognitive deficits about one year after CHT (21.2% in 2 or more neuropsychological parameters). The degree of neuropsychological impairment at T1 (that is, the number of deficitary test scores) was the key predictor for cognitive status at T3. Our data indicate the possibility of persistent deficits in a subgroup of breast cancer patients after adjuvant CHT. These patients need differentiated and empirically evaluated cognitive rehabilitation strategies. We propose, in light of our present knowledge, an integrated and individualzed concept to that end - one combining functional training to improve attention and memory, the development of everyday compensatory strategies, and behavioural therapeutic approaches in dealing with any residual deficits. At the present time individual clinical case studies (Cicerone et al., 2000) are a reasonable alternative to control group study designs when the empiric examination of such interventions is being considered.

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