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Short-term monitoring of cognitive functions before and during the first course of treatment

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Abstract *Purpose*: Side effects of chemotherapy on cognitive functions in older patients have rarely been investigated. Addressing this lack of research, the present study evaluated cognitive functions in older cancer patients. *Methods*: A total of 130 younger ($n = 59$; age < 60) and older ($n = 71$; age≥60) cancer patients with hematological disease or cancer of the intestinal tract took part in the study. To explore short-term effects of chemotherapy, a group of patients assessed before the start of chemotherapy was compared with patients who already received their first course of chemotherapy. *Results*: Cognitive impairments of verbal learning, word fluency, and memory were observed following the first few days after treatment onset. Older patients showed stronger memory impairments after start of chemotherapy than younger cancer patients. Additionally, depression was neither associated with short-term effect of chemotherapy nor with age. *Conclusions*: The results suggest that chemotherapy has negative short-term effects on some cognitive functions. But age-dependent effects were only found for memory.

Keywords Older cancer patients · Cognitive impairments · Chemotherapy · Depression · Gender

Introduction

Incidence and mortality of cancer increases significantly with age (Schonwetter 1992; Monfardini and Yancick 1993; Roche et al. 1997). Considering the growing geriatric population in Western societies, cancer in old age will be a prominent future challenge for medical and psychological treatment. General physical conditions, co-morbidities, pharmacological as well as psychological and cognitive factors have to be considered in order to provide the optimal treatment for older cancer patients.

So far, only a few studies have investigated cognitive functions following chemotherapy in adult patients, notably in breast cancer patients (Wieneke and Dienst 1995; Van Dam et al. 1998; Schagen et al. 1999; Brezden et al. 2000). These studies give evidence that adjuvant chemotherapy may result in significant cognitive impairments in patients with breast cancer. The degree of cognitive impairment was demonstrated to follow a dose function of chemotherapy. When groups exposed to a high-dose chemotherapy were compared to groups receiving a standard-dose chemotherapy, patients exposed to higher doses of chemotherapy showed more severe cognitive deficits than those with low doses of therapy. In addition, the decrease of cognitive functions was positively correlated with the duration of chemotherapy but unrelated to the type of chemotherapy or to depression (Wieneke and Dienst 1995; Brezden et al. 2000).

Although only little is known about the cognitive consequences of chemotherapy in old age, there is some evidence for an age-dependent detrimental effect of chemotherapy on cognitive functions. In a series of prospective clinical trials, Taylor et al. (1998) evaluated the effects of cranial radiotherapy and chemotherapy on cognitive performance in glioma patients by the use of the mini-mental-status examination (MMSE). Patients with a substantial decrease of the MMSE score were significantly older than those with no decrease of scores 6 months after treatment onset.

Many studies support the notion that the aging population is confronted with an increase of physical and psychological disabilities and serious diseases. Additionally, many studies have shown that older people have less physical resistance as well as somatic and

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psychological resilience than younger individuals to cope with physical illness, social and interpersonal change, and the cognitive restrictions that emerge from the common process of aging. These age-related restrictions of physical and psychological functioning have great impact on the ability of individuals to function properly in daily life while aging (Ershler and Balducci 1994). In addition the course of senescence also affects the neurophysiological, endocrinological, immunological, and gastrointestinal responses and tolerance against prescribed drugs and the pharmacokinetics of drugs for anticancer treatment. Chemotherapeutic drugs might have different positive and negative effects in physically and psychologically frail elderly than in younger individuals with similar physical disease. These drugs might also have a different impact on a number of CNS functions that are basic for the management of daily life and resilience against the burden of cancer. Since chemotherapeutic drugs are considered to be toxic not only to cancer-affected cells but to all cells including those of the CNS, one has to assume that older cancer patients are at higher risk than younger individuals to develop cognitive impairments following chemotherapy.

Therefore, this study was aimed examining whether chemotherapy has cognitive side effects and whether more serious cognitive side effects exist in older than in younger cancer patients following chemotherapy. We investigated short-term effects of chemotherapy on the cognitive performance in older and younger cancer patients at the time of diagnosis and during treatment.

Patients and methods

Patients

One hundred and thirty cancer patients with malignant hematological diseases or cancer of the gastrointestinal tract treated at the Department of Internal Medicine of the Friedrich-Schiller-University (FSU) of Jena participated voluntarily in the present study (Table 1). The group of patients consisted of 59 younger (between 18 and 59 years) and 71 older (60 years plus) patients.

Each patient received standardized information about the study and gave written informed consent. The study was approved by the Ethics Committee of FSU.

In order to participate, patients had to fulfil the following criteria: they had (1) no evidence of metastasis related to CNS, (2) no surgery within 4 weeks prior to the start of participation in this study, (3) no history of neurological or psychiatric symptoms, (4) no use of medication that might interfere with the chemotherapy prescribed and no use of any medication for which side effects were known to affect cognitive functioning, and (5) no abuse of alcohol or drugs.

Procedures and measures

All patients were recruited by their oncologists. A battery of neuropsychological tests covering a broad range of cognitive functions was used (Eberhardt 2003). Testing took approximately 1 h.

Word generation was assessed by a subtest of the Dementia test (Kessler et al. 1999). This subtest involves a simple task requiring the generation of words from a specific semantic category within a limited period of time. A typical task is to enumerate as many supermarket products as possible within 1 min. Impairments of such word generation are typical for lexical disorder and are commonly observed at the beginning of dementia. Higher test scores correspond to better performance (word generation).

Attention and memory were assessed by the Syndrom-Kurz-Test (SKT). This test provides a measure of attention and memory disorder in dementia and cerebral insufficiency (Erzigkeit 1992). It consists of nine subtests reflecting attention and memory functions with a special focus on perceptual and psychomotor speed. Higher scores correspond to lower performance (attention and memory).

Capacity of verbal and nonverbal learning functions was assessed by the verbal (VLT) and nonverbal learning tests (NVLT) (Sturm and Willmes 1999). Higher scores of both tests correspond to better performance (*verbal learning*, *nonverbal learning*).

Thinking and reasoning, i.e., logical reasoning in particular, was assessed by subtest three of the Leistungspruefsystem (LPS) (Horn 1983). An age adjusted test form of this subtest (LPS 50+) was used in older patients (Sturm et al. 1993). Higher scores indicate better performance (*logical reasoning*).

Table 1 Gender, age, dose of chemotherapy, and diagnosis

		Older patients	Younger patients
Gender	Female (*n*)	32	23
	Male (*n*)	39	36
	Total (*n*)	71	59
Age	M (SD)	69.1 (6.6)	45.0 (12.2)
Diagnosis	Malignant hematological diseases (*n*)	37	35
	Cancer of the gastrointestinal tract (*n*)	34	24
Dose of chemotherapy[a]	Low (*n*)	5	3
	Medium (*n*)	26	13
	High (*n*)	4	18

M mean score, *SD* standard deviation, *n* number of patients
[a]Patients with baseline after start of chemotherapy

Additionally, a questionnaire was used to assess *depression*. Depression is a well-known factor affecting cognitive performance in response to a life-threatening disease like cancer (Moffic and Paykel 1975; Rodin and Voshart 1986; Massie 1990; Valente and Saunders 1996; Aragona et al. 1997; Chibnall 2002; Gallagher et al. 2002; Smith et al. 2002). Earlier studies attributed cognitive symptoms of cancer to emotional consequences of the disease rather than to treatment factors (Oxman and Silberfarb 1980; Silberfarb 1983; Silberfarb and Oxman 1988). More recent studies have also emphasized the importance of psychological factors for the cognitive dysfunctions of cancer patients (Cull 1990; Cull et al. 1996; Bruera et al. 1992; Valentine et al. 1998). Depression was assessed by a German version of the beck depression inventory (BDI). It was used to control the confoundation of test performance by depression (Hautzinger et al. 1995). Higher scores of the BDI correspond to higher levels of depression.

Design of the study

This study was part of a long-term study concerning the course of cognitive functions of patients receiving chemotherapy over a time of 2 years. Here only the baseline evaluations are reported. Due to institutional and logistical reasons it was impossible to investigate all patients before the start of chemotherapy. Due to the severity of cancer, it was necessary in some cases of younger and older cancer patients to start the treatment immediately after initial diagnosis, i.e., before baseline assessment could be arranged with the neuropsychologists. Consequently, two independent groups of younger and two independent groups of older patients were formed to evaluate the impact of short-term chemotherapy on cognitive functions. In the first group of younger patients and the first group of older patients, baseline testing took place after diagnosis but *before the beginning of chemotherapy* itself (baseline before chemotherapy, BBC). In the second group of younger patients and the second group of older patients, baseline testing took place *after the beginning of chemotherapy* (baseline after start of chemotherapy, BAC) but on average within the first 5 (± 3) days after the start of chemotherapy. BCC and BAC groups were formed in a nonrandomized fashion but in dependence on treatment initiation.

Statistics

Version 11.5 of the statistical package for social sciences (SPSS) for Windows was used for all statistical analyses. The four independent groups of patients were checked for differences in demographic, medical, and depressive characteristics by either chi-square tests for categorical variables or by Student's t tests for independent groups of metric variables. Statistical evaluations of the short-term effects of chemotherapy were performed by univariate analyses of variance (ANOVA) using the between-subject factors *group* (younger vs. older patients), *time of baseline examination* (BBC vs. BAC), and *gender* (female vs. male). Dependent variables were the scores of the neuropsychological tests for word generation, attention and memory, verbal and nonverbal learning, logical reasoning, and depression.

Results

Characteristics of patients

The sociodemographic characteristics (number of patients, age, educational level, and professional training), medical characteristics (diagnosis, general performance status measured by Karnofsky scale, and treatment modality assessed by a three-level rating scale), or depression of the two groups of younger patients (BBC and BAC) were statistically not different from each other. The same was true for the two groups of older patients (Table 2). However, significant differences were observed between male and female older patients: the sample included 11 women and 23 men in the older BBC group and 21 women and 16 men in the older BAC group ($\chi^2 = 4.262$; $df = 1$; $P = 0.039$). In contrast gender was equally distributed within groups of younger patients ($\chi^2 = 2.022$; $df = 1$; $P = 0.155$).

Medical diagnoses of younger and older patients did not differ significantly from one another ($\chi^2 = 0.68$; $df = 1$; $P = 0.410$). Both groups were equally composed of patients with intestinal tract and hematological diseases ($\chi^2 = 0.001$; $df = 1$; $P = 0.978$). This was also true for both subgroups of older patients (older BBC vs. older BAC: $\chi^2 = 1.18$; $df = 1$; $P = 0.278$).

However, there were significant differences in the doses of chemotherapy between younger and older cancer patients (BAC: $\chi^2 = 13.73$; $df = 2$; $P = 0.001$): Younger patients were mostly treated with a high-dose chemotherapy while older patients mostly received a medium-dose chemotherapy. Dose of chemotherapy protocols was assessed by a three-level rating scale (high-, medium-, low-dose), which was developed and applied by clinical oncologists of the Department of Internal Medicine of FSU. Ratings were based on quantity and quality of adverse reactions associated with the treatment regime.

Statistical results of short-term effects

Compared to patients with BBC those with BAC showed significantly reduced cognitive performances (main effect: time of baseline examination) in word generation ($F_{(1,121)} = 4.29$; $P = 0.041$), memory ($F_{(1,118)} = 5.10$; $P = 0.026$), and verbal learning ($F_{(1,119)} = 7.62$; $P = 0.007$) (Table 3). A significant interaction between factors group of patients and time of

Table 2 Statistical comparisons in sociodemographic characteristics, medical characteristics, or depression between the two groups of younger and older patients (BBC and BAC)

	Older patients	Younger patients
Number of patients	$\chi^2 = 1.48$; $df = 1$; $P = 0.22$	
Age	$t = 0.26$; $df = 69$; $P = 0.80$	$t = 1.06$; $df = 57$; $P = 0.30$
Educational level	$\chi^2 = 7.64$; $df = 4$; $P = 0.12$	$\chi^2 = 5.63$; $df = 3$; $P = 0.13$
Professional training	$\chi^2 = 2.80$; $df = 4$; $P = 0.59$	$\chi^2 = 2.08$; $df = 4$; $P = 0.72$
Diagnosis	$\chi^2 = 1.18$; $df = 1$; $P = 0.28$	$\chi^2 = 0.001$; $df = 1$; $P = 0.98$
General performance status	$\chi^2 = 4.12$; $df = 5$; $P = 0.53$	$\chi^2 = 2.92$; $df = 3$; $P = 0.40$
Dose of chemotherapy	$\chi^2 = 0.45$; $df = 2$; $P = 0.80$	$\chi^2 = 2.56$; $df = 2$; $P = 0.28$
Depression	$\chi^2 = 1.17$; $df = 1$; $P = 0.28$	$\chi^2 = 0.57$; $df = 1$; $P = 0.45$

χ^2 chi-square-tests, *t t* tests for independent groups, *BBC* baseline examination before first chemotherapy, *BAC* baseline examination after first chemotherapy

baseline examination ($F_{(1,118)} = 5.79$; $P = 0.018$) for *memory* functions revealed significant lower memory scores of older BAC patients as compared to older BBC patients ($t = -3.04$; $P = 0.003$). In contrast, *memory* performance of the BCB and BAC groups of younger patients did not differ significantly from each other (Fig. 1). All other cognitive functions (attention, nonverbal learning, logical reasoning) and depression indicated no significant short-term effect of chemotherapy neither in older nor in younger patients.

Furthermore, male patients showed lower performances than female patients in word generation (male: $M = 18.50$; SD = 5.55 vs. female: $M = 21.42$; SD = 6.11; $F_{(1,121)} = 8.74$; $P = 0.004$) and memory (male: $M = 1.66$; SD = 1.45 vs. female $M = 1.33$; SD = 1.35; $F_{(1,118)} = 4.20$; $P = 0.043$) independently of age. However, older patients scored generally lower (main effect of group) in word generation ($F_{(1,121)} = 5.51$; $P = 0.021$), memory ($F_{(1,118)} = 13.18$; $P = 0.0001$), logical reasoning ($F_{(1,106)} = 22.09$; $P = 0.0001$), and nonverbal learning ($F_{(1,92)} = 4.94$; $P = 0.029$) than younger patients.

When depression scores were used as covariate, the analysis revealed a significant association of depression with nonverbal learning ($F_{(1,92)} = 10.32$; $P = 0.002$). Nonverbal learning performance correlated negatively with depression ($r = -0.33$; $P = 0.001$) with lower performance scores being associated with higher depression scores.

Additional analyses were undertaken to assess possible dose effects of chemotherapy on short-term treatment effects. Due to small sample sizes of BAC patients with low- and high-dose chemotherapy it was not possible to include the factor *dose of chemotherapy* into the ANOVA. However, an additional univariate ANOVA for patients who received medium-dose chemotherapy using the between-subject factors group (younger vs. older patients) and time of baseline examination (BBC vs. BAC) was performed to control for possible dose-dependent treatment effects on cognitive functions. Scores of all neuropsychological tests with significant results in the initial analysis served as dependent variables. Results revealed a significant interaction between factors group and time of baseline examination ($F_{(1,66)} = 6.437$; $P = 0.014$) for memory functions, but not for word generation and verbal learning. The interaction between group and time of baseline examination resulted from lower memory scores ($t = -2.37$; $P = 0.023$) in older BAC patients ($M = 2.42$; SD = 1.74) as compared to older BBC patients ($M = 1.30$; SD = 1.30). In contrast, performance was not significantly different between both groups of younger patients. There were no significant main effects of factors group and time of baseline examination in all further analyses using the dependent variables memory, word generation, and verbal learning.

Table 3 Short-term effects of chemotherapy

	Older patients						Younger patients					
	BBC			BAC			BBC			BAC		
	M	SD	*n*	*M*	SD	*n*	*M*	SD	*n*	*M*	SD	*n*
Word generation	19.62	5.31	34	17.33	6.49	36	21.59	5.25	22	20.49	5.91	37
Attention[a]	1.24	1.54	33	2.14	3.29	35	0.81	1.12	21	1.38	2.03	37
Memory[a]	1.36	1.34	33	2.49	1.67	35	1.14	1.32	21	0.97	0.99	37
Verbal learning	22.54	8.53	26	21.22	9.20	27	28.37	6.33	16	22.09	6.92	33
Nonverbal learning	12.50	8.17	26	14.41	9.14	27	19.31	7.26	16	16.63	5.86	32
Logical reasoning	15.90	5.70	29	14.18	5.29	28	22.00	6.53	21	19.11	6.17	36
Depression	8.38	6.04	26	9.25	7.54	28	5.29	4.17	17	7.85	4.41	33

M mean score, *SD* standard deviation, *n* number of patients, *BBC* baseline examination before first chemotherapy, *BAC* baseline examination after first chemotherapy

[a]Higher mean scores corresponded with lower performance

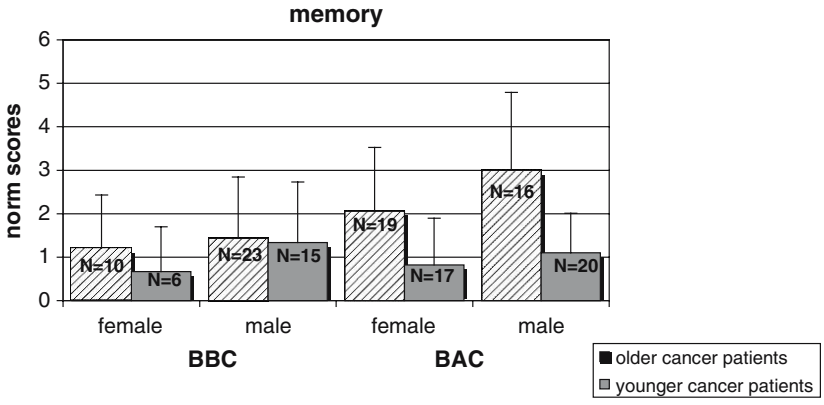

Fig. 1 Memory-performance scores at baseline (*BBC* baseline examination before first chemotherapy, *BAC* baseline examination after first chemotherapy) for older and younger patients (the lower the score, the better the memory performance; *numbers in columns* indicate number of patients per group)

Discussion

Our results indicate that the exposure to chemotherapy has significant negative short-term effects on a small number of cognitive functions in younger and older cancer patients, including word generation, memory, and verbal learning. In one of these functions, i.e., for memory, older patients showed stronger impairments immediately after the start of chemotherapy than younger patients.

These *immediate effects of chemotherapy* are in line with previous observations indicating significant cognitive impairments in verbal and visual memory functions as well as speaking performance after the initiation of treatment in cancer patients (Wieneke and Dienst 1995; Brezden et al. 2000). Moreover, Wieneke and Dienst (1995) described therapy-induced deteriorations of mental flexibility and information processing, visual spatial abilities, motor function, and attention and concentration. In contrast, attention and concentration were not affected by chemotherapy in the present study. One reason for this difference might be that the tests used in the present study to identify cognitive disorders were not sensitive enough to identify subclinical deteriorations. The tests used by Wieneke and Dienst (1995) allowed to identify performance slightly below average. We also observed slightly, but not significantly lower values for attention and concentration; however, these changes did not reach significance in the present study. Another reason for the discrepancy between our and the Wieneke and Dienst (1995) study might be related to the association between test performance and the type of cancer. In both studies, patients were not compatible with regard to diagnosis and treatment. However, it remains a relevant issue of further studies whether differences in diagnosis and therapy represent significant factors that negatively affect cognitive functions in different ways.

Age-dependent short-term effects of chemotherapy were only found for memory. Older patients exposed to a first circle of chemotherapy (i.e., the BAC group) showed lower performance of memory than older cancer patients who were not yet exposed to chemotherapy (i.e., the BBC group), while younger patients before and after the first few days after the initiation of chemotherapy showed no significant decrease. It is important to note that unless cognitive functions were deteriorated by chemotherapy, the scores for most cognitive functions in older patients were still in the range of only mild impairments. Our data are in line with an age-dependent increase of dementia being observed in patients during chemotherapy of lymphoma (Balducci et al. 1989). Moreover an analysis of only those patients who received a medium-dose chemotherapy showed a significant impairment of memory in older age as compared to younger patients, i.e., the result of memory impairment in older age was probably not a consequence of different doses of chemotherapy. A possible explanation for memory impairments could be the greater toxicity of chemotherapy in old individuals (Baker and Grochow 1997; Sekine et al. 1998).

Clear *overall cognitive differences between younger and older patients* were observed independently from the time of chemotherapy administration: Older patients exhibited always lower performances in word generation, memory, logical reasoning, and nonverbal learning than younger patients independently of whether treatment was started already or whether treatment was not started yet. All these cognitive variables concern cognitive functions related to fluid intelligence which has been found to deteriorate relatively linearly as a function of age (Lindenberger and Baltes 1995; Mayer and Baltes 1999). The data presented here are consistent with this observation.

A further result was the *gender difference* in word generation and memory performance. Male participants revealed lower performance than female participants, a result that is well documented as a general function of gender (Hyde and Linn 1988; Halpern 1992; Schaie and Willis 1993; Herlitz and Yonker 2002; Colley et al. 2002), especially for tasks affording verbal-episodic memory (Herlitz and Yonker 2002).

Depression had no general effect on cognitive performance in our study. Furthermore, the test scores for depression were far below the cut-off point for clinically relevant affective disorders. Thus, our data are consistent with the observation that the prevalence of

depression in cancer patients is not higher than in the general population (Massie 1990).

Finally, a critical question of our study is the fact that cohorts were rather small and unbalanced in size. Moreover, the two study cohorts were formed in a nonrandomized fashion. Therefore, the internal validity of the results is limited. The data give some information about cognitive functioning in cancer patients but they should be considered as preliminary results.

Another point that should be taken into consideration is that patients of the BAC cohort might have been suffered with more advanced, even life-threatening disease. Possibly, the differences observed between the study's cohorts might be a consequence of differences in the severity of cancer disease. However, there is some evidence against such an assumption: First, both groups (BBC and BAC) do not differ in general performance state measured by Karnofsky scale (see Statistical results of short-term effects); second, there are no statistical differences between BBC and BAC in diagnoses (see Statistical results of short-term effects and Table 1); third, there are no differences in cognitive functions between parts of these groups after 6 months (Eberhardt et al. 2005). The results of Eberhardt et al. 2005 suggest that chemotherapy has no negative effects on cognitive functions after the first 6 months following treatment onset. At this time point, cognitive functions demonstrated to be completely recovered independently of patient's age.

In summary, our data demonstrate that older compared to younger cancer patients were not more vulnerable for impairments of all assessed cognitive functions except memory at the start of chemotherapy. Since our data are based on nonbalanced and not randomized cohorts data should be interpreted as preliminary. Double-blind, randomized, balanced and longitudinal studies are needed to provide more valid results.

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