RESEARCH ARTICLE

ACTA Vol. 12, No. 4, 2014, 417-427
NEUROPSYCHOLOGICA

Received: 12.09.2014
Accepted: 20.12.2014

A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

DOI:10.5604/17307503.1138845

IMPACT OF CHEMOTHERAPY ON MEMORY, ATTENTION AND EXECUTIVE FUNCTIONS DEPENDING ON THE STAGES OF TREATMENT AND THE LEVEL OF DEPRESSION IN FEMALE PATIENTS WITH CANCER

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SUMMARY

Background: This study examined the neuropsychological effects of chemotherapy on female cancer patients' cognitive processes, depending on their stages of cancer treatment and mood (level of depression).

Material/ Methods: The study included 90 women, aged 18 -72: 45 female patients with cancer treated with chemotherapy and 45 matched healthy subjects. The patients were classified into three stages of therapy: Initial Stage – a maximum of 3 cycles of chemotherapy, Chronic Stage – 4 to 6 chemotherapy cycles and Recurrence and/or Metastasis – a maximum of 2 cycles during the second bout of the disease. The methods used were: the Rey 15-Item Memory Test, the Attention and Perceptiveness Test, the Tower of London Test and the Beck Depression Inventory.

Results: The results indicated a higher intensity of depression in the group of patients. Processes of verbal memory and attention focused on verbal stimuli occur correctly in patients. We found a lower rate and precision in visual perception, slower operation rate, inhibition impairments, but an effective process of planning in the group of patients in comparison with the controls. We did not find any significant impact on the part of emotional state on the cognitive effects of chemotherapy in patients. The Chronic Stage of chemotherapy is a risk factor for the emergence of psychomotor retardation.

Conclusions: Cognitive functions are altered in female patients receiving chemotherapy, which confirmed the existence of the phenomenon of chemobrain. The effects of chemotherapy do not show as specific impairments in the processes of selective cognitive functions and the impact is of a non-specific nature.

Key words: chemobrain, stage of cancer treatment, cognitive dysfunction, depression

BACKGROUND

Issues related to the psychological effects of cancer treatment, including the impact of chemotherapy on patients' cognitive processes, are significant from the point of view of both theory and application (Ogińska – Bulik, 2013). Impairments of cognitive functioning have been reported in several studies in patients treated with chemotherapy. The adverse effects of chemotherapy are referred to as post-chemotherapy cognitive impairment (PCCI), chemotherapy-induced cognitive dysfunction, chemobrain, and chemofog (Ahles & Saykin, 2007; Jansen et al., 2011; Raffa et al., 2006; Staat & Segatore, 2005).

Cognitive deficits have been found in females receiving supplementary treatment for breast cancer, patients with lung cancer, head and neck tumours, testicular cancer, lymphoma, multiple myeloma, prostate cancer, in patients following hematopoietic cells transplantation, and in those with carcinoid syndrome (Tannock et al., 2004; Szafryna–Kliwicka & Litwiniuk, 2011).

Incidence of cognitive impairments in a group of people diagnosed with neoplastic diseases is in the range of 17 to 75% (Ahles et al., 2002; Wieneke & Dienst, 1995; Schagen et al., 1999). However, some publications have also shown that no such deficits occur (Donovan et al., 2005). Contradictory data, among other thin gs, result from the different methodologies applied by various studies (Szafryna–Kliwicka & Litwiniuk, 2011).

Additionally, an in-depth investigation of this phenomenon is further complicated by the large number and diversity of the variables affecting the manifestation of chemobrain symptoms; such factors include fatigability, depressions, education, life experience and the personal circumstances of specific patients (Hede, 2008). Previously reported effects of chemotherapy included defects in such domains as: working memory, psychomotor speed, reaction time, visuospatial abilities, verbal fluency, ability to perform complex activities, flexibility in thinking, visual and verbal memory (Tannock et al., 2004) attention, speed of visual analysis and synthesis, as well as in visual-motor coordination (Pietrzyk, 2010).

Empirical data suggest there is no link between the type of administered cytostatic agents and the quality of cognitive dysfunction (Szafryna–Kliwicka & Litwiniuk, 2011; Heflin et al., 2005).

Specific patients are found with a significantly varied intensity of cognitive dysfunctions, where the symptoms range from subtle, hardly perceptible disturbances to considerable neurological dysfunctions affecting the quality of life. For instance, Jenkins et al., demonstrated that only a small percentage of women receiving adjuvant treatment for breast cancer experienced objective, measurable changes in memory and focused attentionlevel, and such problems were found to have a short-term effect (Jenkins et al., 2006). Other longitudinal studies related to breast cancer treatment identified subtle deficits in verbal fluency and verbal memory, accompanied by the normal functioning of other cognitive processes (Quesnel et al., 2009).

Contradictory findings are also related to the duration of effects. In most cases cognitive dysfunctions are transitory (Schagen et al., 2006). A study demonstrated that, following treatment with cisplastin combined with etoposide, the symptoms of chemobrain were less pronounced in 60% of patients several weeks after the therapy, and seven months later they had disappeared altogether in most patients (Donovan et al., 2005). In the case of some individuals, the adverse effects of chemotherapy, such as attention deficit or dysfunction in short-term memory, persisted for many years after the treatment, which means that the harmful effect of cytostatic agents may permanently affect the brain (Wefel et al., 2010). The adverse impact of chemotherapy may also be observed in the form of changed brain functions, as demonstrated by neuroimaging tests (Tannock et al., 2004) Such changes were mainly found in the frontal lobes, hippocampus, thalamus, cingulate gyrus, and caudate nucleus (Szafryna–Kliwicka & Litwiniuk, 2011).

The development of chemobrain is promoted by genetic predispositions. Moreover, the probability of chemobrain symptoms is increased with the use of cytostatic agents which cross the blood-brain barrier, namely: methotrexate, fluorouracil, Vinca alkaloids, bleomycin, cisplatin, cyclophosphamide, hydroxyurea, procarbazine, anthracyclines (De Walden-Gałuszko, 2011). Hence, the mechanisms underlying chemobrain development seem to include: direct damage to neurons caused by cytostatic agents crossing the blood-brain barrier (Raffa et al., 2006) altered metabolism in CNS due to chemotherapy, decreased activity of neurotransmitters, damaged DNA and shortened telomeres, and the release of proinflammatory cytokines. It was demonstrated that even if a cytostatic agent itself does not cross the blood-brain barrier, it causes the activation and release of cytokine (TNF-α) into the bloodstream; higher concentrations of this cytokine were found in the brain tissue of experimental animals. The accumulation of TNF-α in neurons, by producing reactive oxygen and nitrogen species, disturbs the functions of mitochondria, and as a consequence leads to apoptosis (Szafryna–Kliwicka & Litwiniuk, 2011). It has been reported that antineoplastic drugs may adversely impact both the self-renewal potential of neural stem cells and chromatin remodelling within the hippocampus; the latter defect may be responsible for the cognitive dysfunctions caused by treatment with cytostatic agents (Briones & Woods, 2011).

Additionally, the risk factors for altered cognitive processes following cancer treatment include: vascular changes, surgical intervention and general anesthesia, hormone therapy, paraneoplastic syndromes, adjuvants used in cancer treatment (painkillers, antiemetics), anaemia, comorbid mental disorders, such as anxiety and depressive disorders, as well as the medications used to treat these (Craig et al., 2014; Argyriou et al., 2011).

As a result of experiments it has also been shown that cytostatic drugs are likely to impair learning and memory processes (Raffa, 2011).

Some findings suggest there is a causal relationship between mood disorder and cognitive deficits (Meyers et al., 2005), while other studies have failed to

confirm this link (Wefel et al., 2010; Ferguson et al., 2007). Yet, the opposite relationship seems more likely: it is indeed cognitive disorders that cause depression and anxiety (Cull et al., 1996). In fact, it has frequently been observed that cognitive complaints occur jointly with anxiety, depression and fatigue (Szafryna–Kliwicka & Litwiniuk, 2011). A relationship has also been found between chemobrain and baseline education level. It is possible that impairments in cognitive function are more frequently shown by individuals with a lower level of education (Quesnel et al., 2009).

To date only a few studies had been published on the effects of mood and no studies on the effects of the stage of treatment as moderators in cognitive functioning in patients treated with chemotherapy.

The present study was designed as an attempt to clarify the impact of chemotherapy on cognitive functions in female patients of oncology wards, by answering the following questions: 1) Do women treated with chemotherapy differ in terms of the quality of cognitive processes from healthy women i.e., those not subjected to chemotherapy? 2) Does the level of depression modify the cognitive functions in females treated with chemotherapy and healthy people? 3) Does the stage of treatment (number of chemotherapy doses) differentiate the quality of cognitive processes in women receiving chemotherapy?

MATERIALS AND METHODS

The study included 90 women, aged 18-72, who were divided into two equal groups – patients with cancer (CP – Cancer Patients) and healthy subjects (HP – Healthy People). The empirical material was collected during the period from July to December 2012. The clinical tests were conducted at *Szpital Specjalistyczny w Brzozowie, Podkarpacki Ośrodek Onkologiczny* (The Brzozów Specialist Hospital – The Podkarpackie Oncology Centre in Brzozów, Poland).

The CP group consisted of 45 female patients treated with chemotherapy. This was the sole way of treatment for these patients. The group was heterogenic in terms of cancer location and the type of chemotherapy administered. The female subjects had been diagnosed with the following medical conditions: Hodgkin's disease (3), breast cancer (21 subjects), multiple myeloma (2), pancreatic cancer (1), rectal cancer (1), follicular lymphoma (1), gallbladder cancer (1), carcinoma of the bronchial tube and lung (3), cervical cancer (1), colon cancer (10), and melanoma skin cancer (1). Taking into account the previous cycles of treatment and the chemotherapy doses received by them, the patients were classified into three stages of therapy: Initial Stage (IS) meant a maximum of 3 cycles of chemotherapy (max 18 doses) – 13 subjects (29%); at the Chronic Stage (CS) there had been 4 to 6 chemotherapy cycles (24 to 40 doses) – 17 subjects (38%); Recurrence and/or Metastasis (SR/M) stands for at least the second bout of the disease (30 to 40 doses during the first bout of the disease, and at least 12 doses after 12 to 24 months from the last cycle) -15 subjects (33%).

Because of the significant age range in the clinical group, controls in HP group were paired with the patients and matched for education and age. The females in HP group did not suffer from oncology and neurology related disorders, had no cognitive complaints, and were not receiving psychiatric treatment.

Neuropsychological tests were conducted separately with each individual, during a single meeting, after informed consent was obtained. The data were collected at the hospital and we only had an opportunity to meet each patient once. That is why we were able to apply only a limited number of methods. The neuropsychological assessment was administered by a trained neuropsychologist. The procedure consisted of three methods covering cognitive domains such as verbal memory, attention and perceptiveness, executive functions and one method covering mood. The Rey Fifteen-Item Memory Test (REY) was used for the assessment of verbal learning and short-term memory. The tool was used to analyze the activity of memorizing and to identify those factors facilitating or hindering the process. It consists of seven trials (Choynowski & Kostro, 1997). The Attention and Perceptiveness Test (*Test Uwagi i Spostrzegawczości* – TUS) version 3/8 was used to measure attention and comprised three indicators: speed of perceptive performance, fallibility of perception and fallibility of attention. The subject was asked to cross off the stimuli given in the instructions (3 and 8) and selected from a number of graphically similar signs belonging to the same set (Ciechanowicz & Stańczak, 2006). The Tower of London Test was administered to assess flexibility in thinking and planning as the components of executive functions. The subject was given a set of three coloured beads placed on pegs of varying length and was asked to recreate the arrangement of beads presented to her on the examiner's board, while observing two rules. The task was to be performed quickly, using the minimum number of moves (Cullbertson & Zillmer, 2001). Importantly, this is an American test which has not been validated for Polish standards, therefore in the present study it was used as an experimental trial. The Beck Depression Inventory (BDI) was used to assess the presence and intensity of depression symptoms, yet this test is not sufficient to identify or exclude depression. BDI takes into account the twenty one most common symptoms of depression (Koppelmans et al., 2012).

Statistical methods

Two-sample *t-tests* for *differences* in the mean, the *two-way* analysis of variance (*ANOVA*) test, the one-way analysis of variance test and post hoc comparisons (Games-Howell Test) were used.

RESULTS

Differences between CP and HP in all investigated variables

At first, the two groups were compared in terms of all the indicators obtained during the study: age, education, emotional state, verbal memory, attention and

Table 1. Comparisons of the group of patients receiving chemotherapy and the group of healthy controls, for the rates of age, education, mood, verbal memory, attention and perceptiveness, and executive functions

Variable	Cancer Patients N=45	Healthy People N=45	Test t	p-value	effect size d
Age	51.1(12.3)	51(12.3)	0.03	0.980	-
Years of education	13.5(3.7)	13.8(3.5)	-0.41	0.682	-
Mood					
Beck Depression Inventory	11.6(7.1)	8.1(5.5)	2.59*	0.011	0.55
Memory					
REY – number of words (in 7 trials)	44.1(9.4)	44,4(8.7)	-0.21	0.835	-
REY – number of perseverations	1.7(1,7)	2.76(2.2)	-2.43*	0.017	0.52
REY – number of confabulations	2.4(2.9)	2.1(2.0)	0.51	0.616	-
Attention and Perceptiveness					
TUS – number of browsed signs	625.1(142.4)	749.6(141.3)	-3.26**	0.002	0.69
TUS – number of errors	0.13(0.34)	0.09(0.3)	0.66	0.508	-
TUS – number of omissions	7.4(6.9)	10(10.3)	-1.43	0.157	-
Executive functions					
TOL – tasks in min. number of moves	3.96(2.1)	3.1(1.7)	2.12*	0.037	0.45
TOL – global timing (seconds)	330.4(124.8)	295.5(100.2)	1.46	0.147	-
TOL – number of broken rules	0.9(1.9)	0.2(0.5)	2.27*	0.027	0.48

*- $p<0.05$
**- $p<0.01$

perceptiveness, and executive functions. The results of the comparison are shown in Table 1.

Due to the assumed approach and the method of selecting the subjects, the two groups did not differ in terms of age and years of education.

The emotional state of the patients and the healthy subjects was different. The females treated with chemotherapy were found to possess more pronounced indicators of depression than the healthy controls.

The assessment of cognitive processes was focused on the functions of verbal memory, attention and perceptiveness as well as executive functions. The rates for memory function in Rey's Test did not show any differences between the groups in the number of both the memorized words and confabulations. Poorer and more varied scores were only found in the control group for the number of perseverations. The medium effect size suggests an average level of relationship between the health condition and this rate.

Comparison of the patients and the healthy females showed that the rates for the processes of attention and perceptiveness (TUS) differed in the number of browsed signs, showing the advantage of the controls, while the effect size was moderate. No other rates differentiated the groups.

Assessment of executive functions (TOL) showed that the number of tasks completed in a minimum number of moves, which indicates correctly performed planning, was higher in the CP group. Similarly, the number of broken rules was also higher in the clinical group. The small effect size in both cases suggests that the relationship between the health condition and rates for executive function is of little consequence.

The impact of depression on the cognitive effects of chemotherapy

In order to verify the hypothesis that cognitive functions are affected by the intensity of depression relative to the health condition, a two-way analysis of variance was conducted according to Formula 3 (intensity of depression: none, mild, moderate, and severe) x 2 (health condition: lack of neoplastic disease, presence of neoplastic disease), where the dependent variable was the level of the selected cognitive functions. No significant effects were found for the rates of verbal memory, on the other hand significant effects were observed in the case of measures of attention and perceptiveness as well as executive functions.

For the rate related to the number of browsed signs in attention test (TUS), analysis of the variance showed the significant main effect of the health condition $F(2. 84)=4.07$ $p<0.05$ $h^2=0.05$, and no effect for mood, and no interaction. In the rate for the number of omissions significant effect relates to the health condition $F(1.84)=7.08$ $p<0.01$ $h^2=0.08$; there is also a significant interaction effect for the level of depression and health condition $F(2.84)=3.48$ $p<0.05$ $h^2=0.08$. Post hoc analysis demonstrated that in the clinical group, individuals differing with depression intensity performed the task at a similar level, and the number of omissions was not significantly varied in their case. On the other hand, the healthy subjects with a varied level of depression differed in their performance of the task – a greater number of omissions coincided with more intense depression.

In the case of TOL, an analysis of variance showed only a significant effect of the health condition for the number of tasks completed in a minimum number of moves $F(1.84)=7.31$ $p<0.01$ $h^2=0.08$, and besides that no effect of mood or interaction of mood and chemotherapy were found.

The effects of the Stage of Treatment on cognitive functions in the patients group

An analysis of variance carried out for the group of patients treated with chemotherapy investigated the effect of the stage of treatment (Initial – IS, Chronic – CS, and Recurrence and/or Metastasis – SR/M) on cognitive functions and emotional state. Chemobrain defined in this way as the relationship between cognitive and emotional functions and the stage of treatment was found to be significant only in one case. Significant differences were found in the global timing in the performance of TOL in the case of patients at different stages of treatment: IS - M=343.0 (108.2); CS – M=384.8 (149.0); SR/M – M= 257.7 (64.1) (test B-F=5,29 p<0,01). A post hoc comparison (Games-Howell Test) demonstrated that patients suffering from a chronic condition significantly differ in terms of global timing in the performance of TOL from those patients with metastasis or a recurrent neoplastic process – they need more time to perform the test (difference in mean values 127.6 seconds, p=0.011).

DISCUSSION

The two groups were matched for age and years of education, which allows for an intergroup comparison related to the investigated aspects of mood and

cognitive functions.

The result obtained for mood indicated a higher intensity of depression in the group of patients. This was fully understandable and predictable. These findings are supported by a number of studies investigating the emotional state of oncology ward patients (Quesnel et al., 2009).

On the other hand analyses focusing on verbal memory processes showed surprising results. Females subjected to chemotherapy and healthy patients memorized an equal number of words and provided the same number of words differing from those in the test. This shows that the processes of verbal memory and attention focused on verbal stimuli occur correctly in these patients. Previously published studies frequently reported memory deficits in persons receiving chemotherapy and conclusions relating to chemobrain have been based on such information (Jansen et al., 2011). Our study does not confirm such deficits. An interesting, and perhaps unusual finding, is the lower number of perseverations observed in the CP group. This suggests a better performance in the relevant task by the patients. We do not suggest this to be a consequence of the positive, stimulating effect of chemotherapy on the patients' brain. Rather that this may be evidence of a high level of motivation to perform a cognitive task. Following multivariate analyses of variance it was determined that this finding is not affected by the health condition, by mood, or by the interaction of these two factors. Therefore the conclusion about the effect of motivations seems justified. In the present study female patients subjected to chemotherapy were found to perform more successfully in this area than the healthy subjects.

Lower scores achieved for the number of browsed signs by the group of patients receiving chemotherapy provide evidence for a lower rate and precision in visual perception. The fact that the patients managed to look through fewer signs may suggest their slower operation rate. The lower scores achieved by the patients group confirm previously reported conclusions about the decreased speed of psychomotor activity (Koppelmans et al., 2012) as a result of chemotherapy.

The number of omissions in TUS is another indicator which provides evidence for conclusions with regard to attention processes. A simple intergroup comparison did not show differences between patients subjected to chemotherapy and the healthy subjects. Yet, further statistical analyses demonstrated that in the CP group, individuals differing in terms of depression intensity performed the task achieving similar scores, which means an increase in the rates for attention did not result from depression, therefore it was to a higher degree linked with the process of cancer treatment. On the other hand, the healthy individuals with varied levels of depression differed in their performance of the task, with more omissions coinciding with more intense depression. This may suggest attention impairments which in patients are mainly a consequence of chemotherapy and in healthy individuals are linked with depression.

Assessment of executive functions (TOL) provided evidence for the effective process of planning in the group of patients, something that was significantly better than in the controls.

It seems explanation of this phenomenon may be similar to that related to the rates of memory – the number of perseverations. Planning is a consciously performed cognitive process, which is controlled by individuals executing a given task, and their performance to a great extent depends on motivation and involvement. The patients receiving chemotherapy were examined on the hospital premises, the trials were preceded by a conversation focusing on psychological issues and establishing a good rapport. According to the patients, for them participation in the study was an opportunity to take a break from the routine of the hospital ward. These factors may serve as an explanation for the better scores achieved by the females receiving treatment in comparison with the healthy subjects, who were not particularly motivated to cooperate. At the same time these data provide evidence for a lack of deficits in these cognitive functions which to a large extent may be impacted by motivation. Yet, there are other processes, such as psychomotor speed, and in the case of the present study specifically the speed of visuospatial perception or the control of impulses and the ability to inhibit responses; these are less susceptible to the impact of consciously controlled processing and to a greater degree depend on biological processes. In the TOL Test the patients subjected to chemotherapy broke more rules and acted more impulsively which shows difficulties relating to response inhibition. Hence, the identified deficits related to these aspects of performance may be treated as a symptom of chemobrain.

The phenomenon of chemobrain was also investigated by comparing the performance of the patients receiving chemotherapy, and classified at different stages of treatment. It was demonstrated that the stage of treatment was a differentiating factor only for the global timing in performance of the test measuring executive functions (TOL). Significant differences were found between the subjects at the chronic stage and at the stage of recurrence/metastasis, where the chronically ill patients needed more time to complete the test than the patients with metastasis or neoplasm recurrence. This finding may suggest that the long term uptake of chemo doses is a risk factor for the emergence of psychomotor retardation, which has been reported during the process of chemotherapy.

This results have some practical implications. Patients treated with chemotherapy should be informed that some symptoms in their cognitive functioning may occur as a side effect of chemotherapy. In these cases, the patients should receive some neuropsychological and psychological support to improve their quality of life (Pachalska et al 2014; Owczarek, 2010).

CONCLUSION

Cognitive functions are altered in female patients receiving chemotherapy, which confirmed the existence of the phenomenon of chemobrain. These changes do not result from emotional factors, such as the depression experienced by patients. The effects of chemotherapy do not show up as specific impairments in the processes of selective cognitive functions and the impact is of

a non-specific nature. This is visible as psychomotor slowing and as difficulties relating to inhibiting behaviours. The Chronic Stage of chemotherapy constitutes a risk factor for the emergence of psychomotor retardation.

ACKNOWLEDGMENTS

The authors would like to sincerely thank all the women who participated in the study at such a distressing period in their life.

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