Original Article

The Relationship between Cognitive Status and Symptom Control in Cancer Patients

Irem Suzer, RN
Tokat Gaziosmanpasa University Hospital, Tokat, Turkey

Nese Uysal, PhD
Amasya University, Faculty of Health Sciences Ipekkoy, Amasya, Turkey

Correspondence: Nese Uysal, PhD, Associate Professor, Amasya University Faculty of Health Sciences Nursing Department, Ipekkoy, Amasya, Turkey E-mail: uysaln2007@hotmail.com

Abstract
Background: Cognitive impairments are a common and negative side effect in individuals receiving chemotherapy.
Objective: This study aimed to determine the cognitive status and symptom control in individuals undergoing chemotherapy and investigate the relationship between them.
Methods: The descriptive research sample consisted of 140 cancer patients receiving chemotherapy at the outpatient chemotherapy unit and medical oncology service of a training and research hospital. Individuals who were newly starting chemotherapy and undergoing chemotherapy were included in the sample. Data were collected using the Personal Information Form, The Edmonton Symptom Assessment System, and the Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog). Data were collected at two time points, before chemotherapy and after receiving four cycles of chemotherapy.
Results: It was found that the total symptom scores significantly increased after four cycles of chemotherapy ($p<0.05$). The scores of "Perceived Cognitive Impairments," "Comments From Others," and "Perceived Cognitive Abilities" were significantly decreases after four cycles of chemotherapy, while no significant changes were found in the scores of "Impact of Perceived Cognitive Function on Quality of Life" ($p>0.05$). A negative and significant correlation was found between the FACT-Cog and the Edmonton Symptom Assessment System scores ($p<0.001$).
Conclusions: Cognitive status is negatively affected during the chemotherapy, and the severity of symptoms contributes to cognitive impairment. It is recommended to monitor the cognitive status of individuals receiving chemotherapy at regular intervals.

Key words: cancer, cognitive function, symptom control

Introduction

Cancer is one of the most common chronic diseases in our country and worldwide. It has been reported that there were 14 million new cancer cases globally and 233,834 cases in Turkey in 2020 (Globacan, 2021). Although cancer treatment varies depending on factors such as the patient's age, tumor localization, stage and general condition, chemotherapy is one of the most commonly used treatment methods (Enç et al., 2017; Haileselassie et al., 2019). Chemotherapy (CT), whether used alone or as a complement to other cancer treatments, inhibits the uncontrolled growth of tumor cells but also damages healthy cells, resulting in local and systemic side effects such as pain, fatigue, nausea, loss of appetite, mucositis, diarrhea, neuropathy, and depression. These problems caused by CT negatively impact individuals' physical and psychosocial well-being, and when these symptoms are not controlled, they may lead to dose reduction or discontinuation of treatment (Genç & Oguz, 2018; Saruhan, 2020). Therefore, minimizing the toxic effects of CT and ensuring symptom control are considered fundamental goals in the care of cancer patients (Lashbrook et al., 2017).

Potential problems associated with CT vary depending on the specific chemotherapeutic agents used, but one of the most significant side effects observed in individuals receiving CT is cognitive dysfunction. Cognitive problems typically manifest as symptoms

such as memory impairment, decreased concentration, impaired thinking ability, and learning difficulties after CT. It has been reported that 75% of cancer patients treated with cytotoxic agents experience cognitive impairment during treatment, and 15-45% of cancer survivors continue to experience cognitive problems months or years after treatment (Asher & Myers, 2015; Chung, 2018). Individuals who experience cognitive problems after CT have difficulty in performing multiple tasks, and their quality of life decreases due to reduced memory and decreased productivity and performance at work. Therefore, early detection of cognitive impairments in individuals receiving CT is crucial within the scope of comprehensive care (Dorland et al., 2016; Ren et al., 2017).

While CTis the primary etiological factors for cognitive problems, the etiology of cognitive impairments is multifactorial. Physical symptoms related to cancer or its treatment, such as anemia, fatigue, and sleep disorders, contribute to cognitive problems (Campbell et al., 2020; Vardy & Haryana, 2017). Studies have indicated that the intensity of psychological symptoms such as depression and anxiety is closely associated with cognitive deterioration (Ren et al., 2017). Chronic pain has been found to cause impairments in various functional domains, including attention, memory, and executive functions. Symptoms such as fatigue, insomnia, and nutritional disorders negatively affect cognitive function by causing a decrease in the number and strength of neural connections (Moriarty et al., 2017; Pendergrass et al., 2019; Schagen et al., 2014). Therefore, symptom assessment is crucial for identifying post-chemotherapy cognitive impairments and associated factors (Ren et al., 2019). Oncology nurses play a critical role as healthcare professionals in assessing cognitive changes and planning interventions to optimize cognitive function (Allen, 2019; Shelton, 2016; Visovatti et al., 2016). Although there are international studies investigating the relationship between cognitive problems and chemotherapy, it has been noted that there is no study investigating the relationship between cognitive problems and symptom control in Turkey (Asher & Myers, 2015; Cui et al., 2021). This study aims to determine the relationship between cognitive status and symptom control in individuals receiving chemotherapy with toxic effects on the nervous system. Research questions are (a) Is there a relationship between cognitive status and symptom control in individuals receiving CT that has toxic effects on the nervous system? (b) Do the cognitive statuses of individuals differ at the start of CT and after the 4th cycle of CT? (c) Do the symptoms experienced of individuals differ at the start of CT and after the 4th cycle of CT?

Methods

Study setting: This descriptive research was carried out at the outpatient chemotherapy unit and medical oncology service of a university hospital between March 20, 2022, and October 1, 2022. The sample of the study consisted of individuals who received CT in the Chemotherapy Unit and Medical Oncology Service and were newly starting chemotherapy treatment. The sample size of the research was calculated using the G*Power analysis program. Based on the study conducted by Lange et al. (2015), the calculation was performed considering the differences in the average scores of Functional Assessment of Cancer Therapy-Cognitive Function, one of the main outcomes of the research, 80% power and 95% confidence interval, with an effect size of 0.85. According to this calculation, it was planned to include 140 individuals in the study (Lange et al., 2015).We included those who are newly starting chemotherapy treatment, aged 18 and above, Turkish-speaking and/or able to read, and gave consent to participate in the research. Chemotherapy treatments were determined as taxane-based drugs (paclitaxel, docetaxel), platinum-based drugs (cisplatin, oxaliplatin, carboplatin), cyclophosphamide, 5-fluorouracil, doxorubicin. We excludedthose whoreceiving palliative chemotherapy treatment, not receiving toxic chemotherapy, have cognitive impairments, with brain metastasis, receiving cranial radiotherapy, and have neuropsychiatric disorders.

Data collection tools: The research data were collected using a Personal Information Form, Edmonton Symptom Assessment System, and Functional Assessment of Cancer Therapy-Cognitive Function.

The personal information form: The form consists of 12 questions regarding the patients' demographic characteristics and their illness and treatments (age, gender, marital status, place of residence, educational level, economic status, diagnosis, duration of diagnosis, chronic diseases, chemotherapy drug, treatment other than chemotherapy).

Edmonton Symptom Assessment System (ESAS)*:* ESAS was developed by Bruera et al. (1991) to evaluate the nine most common symptoms (pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath) in cancer patients. The severity of the symptoms in the scale is assessed on a scale of "0 to 10," where "0" indicates the absence of the symptom and "10" indicates the most severe perception of the symptom. As the score obtained from the scale increases, the severity of the experienced symptom also increases. The validity and reliability analysis of the scale in our country were conducted by Sadirli and Unsar (2009) with cancer patients, and the Cronbach's alpha value was determined as 0.76.

Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog):FACT-Cogis a 37-item measurement tool designed to assess cognitive complaints in cancer patients and consists of four subscales: Perceived Cognitive Impairments (20 items), Impact of Perceived Cognitive Function on Quality of Life (4 items), Comments from Others (4 items), and Perceived Cognitive Abilities (9 items). Individuals respond to each item using a 5-point Likert-type scale, referring to the past 7 days. The higher the total score, the better the cognitive functioning and the lower the impact of cognitive impairment on the patients' quality of life. The validity and reliability study of the scale in our country were conducted by Atasavun Uysal et al. (2021) with cancer patients, and the Cronbach's alpha value was determined as 0.82 (Atasavun et al., 2021).

Data collection: The research was conducted between March 20, 2022, and October 1, 2022, with individuals who received CT that has toxic effects on the nervous system? and were about to undergoing their first CT in a university hospital. In the literature review conducted by the researchers, chemotherapy agents with toxic effects and the potential to cause cognitive problems were identified (taxane-based drugs (paclitaxel, docetaxel), platinum-based drugs (cisplatin, oxaliplatin, carboplatin), cyclophosphamide, 5-fluorouracil, doxorubicin), and individuals were included in the study accordingly (Chiu et al., 2019; Ren et al., 2019). Data collection forms were collected by the researcher before CT and after fourth CT. The interviews lasted approximately 20 minutes. Out of the 287 individuals reached during the data collection process, 42 were not receiving CT that has toxic effects on the nervous system?, 86 had not newly started CT treatment, 6 had neuropsychiatric disorders, and 4 did not give consent, so they were excluded from the study. Additionally, 5 individuals passed away during the data collection process, 2 individuals discontinued chemotherapy treatment, and 2 individuals did not complete their final tests, so they were excluded from the study. The study was completed with 140 individuals who met the inclusion criteria and provided consent.

Ethical approval: Ethical approval was obtained from the non-interventional clinical research ethics committee of a university (Date: 12.01.2022, Decision No: 06). Institutional permission was obtained from the hospital where the research was conducted. Written and verbal consent was obtained. The research was conducted in accordance with the principles of the Helsinki Declaration.

Statistical analysis: The research data were analyzed using the SPSS 18 software program. The Wilcoxon signed-rank test was used for dependent two-group comparisons. The relationship between continuous variables was examined using the Spearman correlation test. The statistical significance level in the study was accepted as $p<0.05$.

Results

The mean age of the participants in the study was 57.36±13.04. It was determined that 52.1% were male, 89.3% were married, 53.6% of the participants had primary education, and 85% evaluated their economic status as "moderate". It was found that 30.7% of the participants had a diagnosis of gastrointestinal system cancer, with average diagnosis duration of 2.7 months, and 40.7% had additional chronic diseases other than cancer.

It was determined that there were significant increases in all symptoms except "depression" after four cycles of chemotherapy. The ESAS total score was calculated as 30.36 before chemotherapy and 41.52 after four cycles of chemotherapy, and this increase was found to be significant ($p<0.001$) (Table 1). It was determined that "Perceived Cognitive Impairments," "Comments from others," "Perceived Cognitive Abilities," and the FACT-Cog total scale score significantly decreased after four cycles of chemotherapy ($p<0.001$) (Table 2). A moderate and inverse significant relationship was found between FACT-Cog total scores and “fatigue”, "drowsiness", "nausea," "appetite", and ESAS total scores. There was a weak-level and inverse significant relationship was found between FACT-Cog total scores and "shortness of breath", "well-being", and "depression" scores ($p<0.05$) (Table 3).

After the fourth cycle of chemotherapy, there was a weak-level and inverse significant relationship was found between FACT-Cog total scores and "fatigue", "nausea", "appetite", and "shortness of breath" scores. There was a moderately significant, and significant inverse relationship was found between FACT-Cog and "drowsiness", "well-being", "depression", "anxiety", and ESAS total scores ($p<0.05$) (Table 4).

Table 1. Results of ESAS Scores

ESAS	**Before CT**	**After 4th CT**	
Symptoms	**Medyan (IQR)**	**Medyan (IQR)**	**p value***
Pain	4(1.5-5)	4(3-5)	**0.001**
Fatigue	3(0.5-5)	4.5(3-6)	**<0.001**
İnsomnia	3(0-4)	4(2-6)	**<0.001**
Nausea	0(0-3)	4(2-5)	**<0.001**
Appetite	2(0-5)	4(2-6)	**<0.001**
Shortness of breath	0(0-3)	1(0-5)	**<0.001**
Well-being	5(3-5)	5(3-6)	**0.021**
Anxiety	4(2-5)	4.5(3-6)	**0.037**
Depression	5(2.5-5)	5(3-6)	0.136
Total ESAS	29.04(18-41)	38.04(29.04-51)	**<0.001**

*Wilcoxon Signed Ranks Test

Table 2. Results of FACT-Cog Scores

FACT-Cog	**Before CT**	**After 4th CT**	
	Medyan (IQR)	**Medyan (IQR)**	**p value***
CogPCI	70.5(63.5-72)	66(54.5-71)	**<0.001**
CogOth	16(15-16)	16(13-16)	**<0.001**
CogPCA	21(19-28)	19(15-23)	**<0.001**
CogQoL	7(4-10)	8(4-10)	0,859
Total FACT-Cog	113.5(104.5-120)	107.5(90.5-119)	**<0.001**

*Wilcoxon Signed Ranks Test Note: Perceived Cognitive Impairments=CogPCI; Comments from Others= CogOth; Perceived Cognitive Abilities=CogPCA; Impact of Perceived Cognitive Function on Quality of Life: CogQoL

Table 3. Relationship between FACT-Cog and ESAS Scores (Before Chemotherapy)

		FACT-Cog				
ESAS		**CogPCI**	**CogOth**	**CogPCA**	**CogQoL**	**Total FACT Cog**
Pain	r*	-0.051	-0.042	-0.188*	-0.111	-0.125
	p	0.548	0.618	0.026	0.193	0.141
Fatigue	r	-0.306**	-0.238**	-0.342**	0.1	-0.278**
	p	<0.001	0.005	<0.001	0.241	0.001
İnsomnia	r	-0.348**	-0.239**	-0.421**	0.067	-0.361**
	p	<0.001	0.004	<0.001	0.435	<0.001
Nausea	r	-0.422**	-0.396**	-0.466**	0.093	-0.410**
	p	<0.001	<0.001	<0.001	0.275	<0.001
Appetite	r	-0.400**	-0.302**	-.424**	0.071	-0.369**
	p	<0.001	<0.001	<0.001	0.405	<0.001
Shortness of breath	r	-0.215*	-0.169*	-0.199*	-0.03	-0.176*
	p	0.011	0.046	0.018	0.724	0.038
Well-being	r	-0.013	0.005	-0.16	-0.426**	-0.207*
	p	0.877	0.951	0.059	<0.001	0.014
Anxiety	r	0.047	0.07	-0.121	-0.432**	-0.163
	p	0.584	0.41	0.156	<0.001	0.054
Depression	r	-0.012	0.041	-0.169*	-0.432**	-0.201*
	p	0.888	0.632	0.046	<0.001	0.017
Total ESAS	r	-0.352**	-0.261**	-0.448**	-0.11	-0.416**
	p	<0.001	0.002	<0.001	0.194	<0.001

*Spearman Correlation test

Table 4. Relationship between FACT-Cog and ESAS Scores (After 4th Chemotherapy)

		FACT-Cog				
ESAS		**CogPCI**	**CogOth**	**CogPCA**	**CogQoL**	**Total FACT-Cog**
Pain	r*	-0.08	-0.036	-0.11	-0.362**	-0.148
	p	0.346	0.67	0.196	<0.001	0.08
Fatigue	r	-0.203*	-0.177*	-0.139	-0.398**	-0.268**
	p	0.016	0.037	0.102	<0.001	0.001
Insomnia	r	-0.236**	-0.195*	-0.185*	-0.347**	-0.313**
	p	0.005	0.021	0.029	<0.001	<0.001
Nausea	r	-0.143	-0.109	-0.073	-0.359**	-0.173*
	p	0.092	0.2	0.393	<0.001	0.041
Appetite	r	-0.155	-0.13	-0.097	-0.312**	-0.186*
	p	0.068	0.126	0.252	<0.001	0.028
Shortness of breath	r	-0.206*	-0.058	-0.107	-0.174*	-0.186*
	p	0.015	0.493	0.209	0.04	0.028
Well-being	r	-0.239**	-0.234**	-0.265**	-0.506**	-0.335**
	p	0.005	0.005	0.002	<0.001	<0.001

Anxiety	r	-0.268**	-0.266**	-0.305**	-0.512**	-0.372**
	p	0.001	0.001	<0.001	<0.001	<0.001
Depression	r	-0.264**	-0.282**	-0.259**	-0.485**	-0.350**
	p	0.002	0.001	0.002	<0.001	<0.001
Total ESAS	r	-0.278**	-0.237**	-0.223**	-0.468**	-0.349**
	p	<0.001	<0.001	<0.001	<0.001	<0.001

*Spearman Correlation test

Discussion

Chemotherapeutic agents cause significant side effects in individuals, including pain, fatigue, nausea-vomiting, loss of appetite, sleep problems, skin and mouth sores, and important adverse effects on the muscle and nervous system. Chemotherapeutic agents also inflict psychological distress such as pain and sadness on individuals and lead to a decrease in their daily role performance (Kurt & Kapucu, 2018). In a study conducted with individuals receiving chemotherapy, it was found that 77.1% of the patients experienced pain and 71.4% experienced anxiety (Dolu Kubilay & Erguney, 2020). In a study, it was found that 12.8% of cancer patients experienced mild fatigue and 40% had moderate fatigue (Usgu & Ozbudak, 2022). In the study conducted by Sargın et al with individuals receiving chemotherapy, it was determined that 32.6% of individuals developed chemotherapy-induced nausea and vomiting (Sargin et al., 2022). Wong et al., (2021), study with cancer patients found that individuals had a general well-being level below the average. In this study, it was found that the severity of symptoms, except for sadness, increased during the chemotherapy process. The increase in cumulative chemotherapy dose due to exposure to chemotherapeutic agents and other potential problems in the cancer process may be a reason for the increased severity of symptoms.

Chemobrain is a problem known as chemotherapy-induced cognitive dysfunction, characterized by memory impairment, slow processing speed, inability to concentrate, and speech difficulties (El-Agamy et al., 2019). In a study with colon cancer patients receiving adjuvant chemotherapy, it was found that chemotherapy had a temporary negative effect on verbal memory (Cruzado et al., 2014). In a study with breast cancer patients using the FACT-Cog scale, it was found that perceived cognitive impairments, perceived cognitive abilities, and quality of life scores before chemotherapy deteriorated during chemotherapy (Myers et al., 2015). In this study, it was found that the average scores of "Perceived Cognitive Impairments", "Comments from Others", and "Perceived Cognitive Abilities" significantly decreased after chemotherapy. The negative effects of chemotherapeutic agents on cognitive functions have been mentioned in the literature, and our research findings are consistent with the literature. The etiology of chemotherapy-related cognitive impairments is multifactorial (Coro et al., 2022). Among the factors other than cancer and cancer treatments that can contribute to chemobrain are symptoms such as stress, depression, fatigue, anemia, loss of appetite, and sleep disturbances (Liou et al., 2019; Yu et al., 2018). In Vardy et al., study with individuals with colorectal cancer, fatigue and cognitive problems were found to be interrelated, too. Fatigue leads to impaired memory and information processing, concentration problems, and decreased cognitive activity (Vardy, 2014). In a study with breast cancer patients, it was found that as the severity of insomnia increased, the perceived severity of cognitive impairment also increased. Insufficient sleep hampers necessary mental rest, which negatively affects cognitive functioning in many ways (Liou et al., 2019).

There is a strong relationship between the cognitive problems reported by individuals and psychological distress (Ren et al., 2017). In a study conducted with breast cancer patients, a significant and negative relationship was found between anxiety and memory and concentration (Scott et al., 2015). Intense stress is believed to create problems in individuals' focus, leading to cognitive problems such as inattentiveness and thought complexity. In a study with

cancer patients, individuals with good appetite showed better emotional and cognitive functions, while individuals with anorexia and early satiety showed worse emotional and cognitive functions (Galindo et al., 2017). Dube et al., study with cancer patients found that as the prevalence of pain increased, there was an improvement in cognitive functions. It is believed that cognitive impairments can occur due to neurochemical changes caused by pain (Dube, 2019). This research revealed a significant relationship between symptoms (pain, fatigue, insomnia, nausea, loss of appetite, shortness of breath, well-being, anxiety, sadness) and cognitive impairment both before chemotherapy and after four cycles of chemotherapy. The research findings indicate a relationship between the severity of symptoms and cognitive impairment.

Conclusion: This research found a significant increase in symptom scores after four cycles of chemotherapy ($p<0.05$). There was a significant relationship between the FACT-Cog scale and ESAS scores both before chemotherapy and after fourth chemotherapy ($p<0.05$). It is recommended to conduct further studies to identify factors and symptoms that may contribute to cognitive impairments in individuals receiving chemotherapy, evaluate cognitive status in a homogeneous sample of cancer patients, increase intervention studies aimed at improving the cognitive status of individuals receiving chemotherapy, and conduct long-term evaluations of cognitive functions after completing chemotherapy.

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