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Effect of cancer treatment on cognitive function in patients receiving chemotherapy: A prospective study

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Introduction

Cognitive dysfunction is one of the mental disorders and is defined as the impairment in the process of understanding such as knowledge, memory power, attention, analysis, judgment, problem solving etc [1-3]. Factors which potentially predispose cancer patients to cognitive dysfunction are depression/anxiety, medications such as corticosteroids, certain anti-emetics, opioids, etc., medical problems including hypothyroidism, anaemia, liver disease, etc, alterations in hormonal levels like deprivation of androgen and estrogen, genetic factors such as Apo lipoprotein E (ApoE), Catechol-O-Methyl Transferase (COMT), inflammatory cytokines, nutritional factors, direct neurotoxic effects of chemo drugs and poor cognitive reserve attributable to age, education, etc [4-6].

Direct neurotoxic effects of chemo drugs is an evident hypothesis for the cause of cognitive impairment following chemotherapy, and so the term chemobrain. Certain chemo drugs like Methotrexate and 5-Fluorouracil are mainly neurotoxic and can cause diffuse white matter changes on neuroimaging. Animal studies have given definite evidence that chemo drugs like Carmustine, Cisplatin, and Cytarabine may be more lethal to white matter progenitor cells and hippocampal stem cells than they are to the target cancer cells [7-10].

Cognitive dysfunction can also be caused by genetic factors in cancer patients [11]. Variants of genes encoding ApoE and COMT have been associated with age-related cognitive decline in the general population. ApoE helps in neuronal repair and plasticity after injury, and one study suggested that long-term cancer survivors with at least 1 ApoE4 allele who were previously treated with chemotherapy had poorer cognitive function. COMT plays a role in the breakdown of catecholamine's [12-14].

Cognitive impairment due to chemotherapy has been reported in 17 to 75% of patients [15]. Though there are numerous rational theories proposing that cancer chemotherapy can be associated with cognitive function impairment, the results of the few studies had observed no relationship to cognitive decline and cancer chemotherapy. With these background, the present study aims to assess the effect of cancer treatment on cognitive function in patients receiving chemotherapy.

Methods

Study design

A Prospective, cross-sectional, observational study was carried out in the department of Medical Oncology, Sri Ramachandra Medical college and Research Institute, Porur, Chennai from October 2016 to November 2017. Study was carried out with the approval of Institutional Ethics Committee, Sri Ramachandra University NO: CSP/16/NOV/52/293.

Study criteria

The study participants were aged not less than 18 years, both genders, diagnosed with any type of cancer and on concurrent chemotherapy regimens for a period of at least 3 months. Patients were excluded if they were on chemotherapy for other conditions which affects their cognitive function such as Alzheimer's disease, neurodegenerative disorders, etc and any subjects unwilling to give informed consent were also excluded.

Sample size

The sample size was calculated using PS-Power and Sample size calculator. Considering alpha- error at 0.05 and 80% power of the study (1-β) with an appropriate 8.5% differences and standard deviation of 0.05 using 1:1 ratio of independent sample t- test, 94 patients must complete the study.

Study procedure

Patients fulfilling the selection criteria were recruited for the study. After getting written informed consent, patients demographic details were obtained in a data collection form. Cognitive function was assessed using Mini Mental State Examination (MMSE) scale. MMSE is used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time; thus making it an effective way to document an individual's response to treatment.

Statistical analysis

Data were analyzed by the SPSS version 16.0. Frequency distribution and percentages were computed for different study variables. The association between various study categorical variables was calculated by using Chi- square test. All p- values were two tailed and significant when values were less than 0.05.

Results and Discussion

A total of 164 patients were included for the study. Majority of them were adults over 45 years (40.9%). The participants were predominantly female patients (71.3%). **Majority of the patients belonged to lower socio economic status.** Out of the 164 patients, 95 patients were in the early chemotherapy cycle, 39 in the middle cycle, and 7 in the late cycle. Chemotherapy was completed by 23 patients. Breast Cancer was the most common type of cancer in the study population (Table 1).

Table 1: Socio-demographic and level of cognitive function of the study patients

Variables	N (%) or mean (SD)
Age (in years)	
18-29	6 (3.7)
30-44	37 (22.6)
45-59	67 (40.9)
>60	54 (32.9)
Gender	
Male	47 (28.7)
Female	117 (71.3)
Socio economic	
Upper	38 (23.17)
Middle	24 (14.63)
Lower	102 (62.19)
Chemotherapy cycles	
Early (3-6 cycles)	95 (57.9)
Middle (7-10 cycles)	39 (23.8)
Late (11-30 cycles)	7 (4.3)
Chemo completed	23 (14)
Type of cancer	
Breast	69 (42.1)
Stomach	14 (8.5)
Cervical	13 (7.9)
Uterus	3 (1.8)
Ovarian	11 (6.7)
Lung	10 (6.1)
Blood	13 (7.9)
Others	31 (18.9)
MMSE level	
Normal	52 (49.05)
Mild	25 (23.58)
Moderate	28 (26.41)
Severe	1 (0.94)

Based on the Mini Mental Scale Scores, patients' cognitive impairment was graded as mild, moderate and severe. Nearly half of the participants had normal MMSE score (45.7%). Correlation between chemotherapy cycles and MMSE scores was tested using Spearman rank correlation. No significant correlation with chemotherapy cycles (Table 2).

Table 3 portrays association between study variables and MMSE score. There is a significant association between gender and MMSE scoring levels. **Similarly there is a significant association between Socio economic status and MMSE levels (p<0.005).** Also Males had a better MMSE score compared to females which was statistically significant.

Table 2: Association between cognition levels and chemotherapy cycles

Cognition Category	N	Mean rank of chemotherapy	P-value
MMSE			0.882
Normal	75	51.92	
Mild	39	57.3	
Moderate	49	53.41	
Severe	1	43.00	

Kruskal Wallis test applied to find the chemotherapy cycles and levels of cognition

Table 3: Association between study variables and MMSE grades

Study variables	MMSE Grades				
	Normal	Mild	Moderate	Severe	P value
Age category					
18-29	4	1	1	0	0.448
30-44	18	8	9	0	
45-59	25	11	14	0	
>60	24	12	14	1	
Gender					
Male	23	16	4	1	0.020*
Female	48	22	44	0	
Socio Economic Status					
Upper	14	8	1	0	0.017*
Middle	1	4	6	0	
Lower	37	13	21	1	
Chemotherapy cycles					
Early (3-6 cycles)	38	16	20	1	0.989
Middle (7-10 cycles)	101	5	6	0	
Late (11-30 cycles)	3	1	1	0	
Chemo completed	12	6	0	0	
Types of Cancer					
Breast cancer	32	10	25	0	0.097
Stomach cancer	5	4	3	1	
Cervical cancer	4	4	5	0	
Cancer of Uterus	0	0	3	0	
Ovarian Cancer	6	3	2	0	
Lung cancer	3	3	2	0	
Blood cancer	16	6	1	0	
Others	15	8	7	0	

Vardy J et al [16] had conducted a prospective longitudinal assessment of cognitive function and fatigue after diagnosis of colorectal cancer (CRC). The study participants were 291 cancer patients with early-stage disease, 72 patients with metastasis and 72 healthy controls. Clinical neuropsychological tests, computer-based Cambridge Neuropsychological Test Automated Battery (CANTAB) and modified Six Elements Test (SET) were used for assessment of cognitive function. Carcinoembryonic antigen, tumour-necrosis factor-α were the blood markers measured. The result of the study was that almost half of CRC patients have cognitive decline

Report tiredness after diagnosis, and report rates are higher than in controls. Women were more prone to cognitive decline than men.

A prospective longitudinal randomized phase 3 treatment trial by Wefel JS et al [17] in 2010 on 42 breast cancer patients who were on 5-fluorouracil, doxorubicin, and cyclophosphamide with or without paclitaxel using FACT-Breast module, neuropsychological tests and mood measures gave the conclusion that acute decline in cognitive function during and/or shortly after chemotherapy occurred in 65% of patients. Late cognitive decline occurred in 61% of patients, with approximately 30% of these patients demonstrating new onset, delayed cognitive dysfunction that was not present earlier.

Jim HSL et al [18] in 2009 had conducted a case-control study on 187 breast cancer patients and an equal number of non cancer controls using the Mental Abilities questionnaire, National Adult Reading Test (NART), California Verbal Learning Test [CVLT], Trails A subtest of the Trail Making Test, Visual Reproduction subtest of the Wechsler Memory Scales-III [WMS-III], Digit Symbol subtest of the WAIS-III. The study concluded that the resulting cognitive deficits noted in breast cancer survivors are relatively subtle and are the result of the general effects of cancer rather than systemic treatment.

A prospective, multi-centre, longitudinal study by Hermelink K et al [19] on 101 breast cancer patients on Epirubicin, paclitaxel, cyclophosphamide, and darbepoetin α using Questionnaire of Experienced Attention Deficits (FEDA), Cognitive Function Scale of EORTC QoL Questionnaire C30, Hospital Anxiety and Depression Scale (HADS) and Neuropsychological tests in 2007 revealed that the patients' reports of cognitive problems increased during chemotherapy, and those problems were not related significantly to cognitive test results but, rather, to anxiety and depression.

Kohli S et al [20] had conducted a multicentre longitudinal study on 595 cancer patients diagnosed with breast, hematologic, GI, lung, prostate, or head and neck cancers in 2007. Cognitive symptoms were assessed using Karnofsky performance status, and the Symptom Inventory and it was found that cognitive impairment is a debilitating and prevalent adverse effect & cognitive problems are associated with cancer and its treatment.

A prospective case-control study was conducted by Stewart A et al [21] in 2007 on breast cancer patients. The study enrolled 61 breast cancer patients on adjuvant chemotherapy and a control group of 51 women who were on adjuvant hormonal therapy. Neuropsychological testing and mood rating scale were used as assessment techniques. The study reported that a threefold greater risk of cognitive decline was found in the chemotherapy patients compared to the hormonal patients.

Conclusion

The present study concludes that low risk of cognitive impairment was observed among the study patients. There is a significant association between gender and MMSE scoring levels. Similarly there is a significant association between socio economic status and MMSE levels. Also males had a better MMSE score compared to females which was statistically significant. To authenticate our report, the study needs to be carried out for longer duration with larger sample size.

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