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Research Article

Evaluation of Perceived Cognitive Impairment Associated with Chemotherapy Among Breast Cancer Survivors in India

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Abstract

Cognitive changes among diagnosed breast cancer patients are often attributed to chemotherapy, without considering other comorbid factors.

The present study evaluates the impact of chemotherapy on cognitive function among breast cancer patients those who were undergoing chemotherapy. The comparison was determined by the variation of the effect of DNA mechanism due to different types of chemo-medicine.

51 women with non-metastatic breast cancer those under-going chemotherapy were evaluated into two groups on the basis their chemo medicine: combination with 5-fluorouracil or without 5-fluorouracil. Cognitive impairment was signified with an assessment of validated Kolkata Cognitive Battery.

The relationship between cognitive function and different combination of chemotherapy along with dosages variation was compared between Group-1 and Group-2. Parsons's "r" correlation revealed in changes of chemo medicine combination with 5FU Medicine: chemo cycle, verbal fluency and time, calculation, word memory Trail 1 and Trail 2 was significantly correlated with variation in chemo medicine. In the group of Chemo medicine combination Without 5FUMedicine: chemo cycle, verbal fluency, Object naming and time, MSE. However, in group 1, verbal fluency, object naming, delayed word memory and delayed word memory recognition were also significantly correlated with dosages variation of chemo-medicine.

In the present study result depicted, variation of chemo-medicine and dosages was associated with poor cognitive function in patients receiving chemotherapy.

Introduction

During and after the chemotherapy treatment some of the cancer patients reported adverse effects of cognitive function such as impaired memory, attention, speed processing, verbal fluency and other different basic cognitive activities [1]. These effects were researched by many scientists through eliciting neurotoxicity of chemotherapy [2]. In 1990, some of the researchers had studied the effect of cognitive function in breast cancer patients who had received chemotherapy. These studies reflected that patients scored lower than expected cognitive performance on the neuropsychological assessment. Almost of 10 years of research had proved the impact of chemotherapy on cognitive function without any reasonable doubt. In first generation of the studies are observational and cross-sectional. So, the obtained results were ongoing and longitudinal. Many perspective studies revealed, cognitive deficit found before taking adjuvant chemotherapy due to these deficits had been transit, induced by surgery and general anesthesia [3]. However, other studies researched baseline status before neo adjuvant chemotherapy compared with untreated breast cancer patients. There cognitive deficit was seen 21% and 30% among patients with untreated breast cancer [4]. On other side, most of the studies had found no evidence of cognitive deterioration among patients who were undergoing chemotherapy by using methodologically sound large scale. In the majority of perspective studies cognitive changes had been seen in some of limited cognitive domains (Sharon M. Castellino *et al.* 2014). Generally, 15%-25% of patients seemed to be affected. Recently, a meta-analytical and neurological studies had presented, after taking chemotherapy treatment among patients with breast cancer cognitive deficits are on average. Still, the researchers had 6 comparisons between subjective complaints and objective neurological assessments. Some of the patients complained the cognitive changes which are not prominent in neurological assessment. Subjective complain of cognitive deficits are strongly correlated with depression, anxiety or other neurological assessment [5]. Even in recent studies had found that subjective cognitive complains are more correlated with depressive symptoms rather than do-main specific neurological assessment [6]. In 2016, researchers conducted a study among patients with breast cancer and age matched healthy control group in comparing cognitive performance before and after chemotherapy. There was shaded light on the problem of cancer-related cognitive impairment (CRCI). CRCI might be related with disease and it's treatment including chemotherapy, hormonal therapy, surgery and radiation [7].

In India, there is not any study about effect of chemotherapy on cognitive function. So, we are unable to establish any study related in West Bengal. We hypothesized that self-reported cognitive difficulties, that is, perceived cognitive impairment, assessed via Kolkata Cognitive Battery (KCB) total score, would be more prevalent among patients with breast cancer those who were undergoing chemotherapy. The score of cognitive functions was researched according to the variation chemo medicine and dosage with single component compared with more than one. Secondly, cognitive function was revised as per reaction of DNA mechanism of each medicine.

Methods and Methodology

Study Design

It was an observational study using validated tools and structured face to face interview.

Sample Selection

This study was conducted at two different tertiary hospitals in Kolkata, situated in eastern India, between May 2017 to August 2017. Early non metastatic breast cancer female participants between age group of 30-60 years, who had at least eight years of formal education were included, after applying specific inclusion and exclusion criteria.

Group 1 and 2

The researchers had approached 236 non metastatic breast cancer patients undergoing chemotherapy; 86 (65.56%) agreed to participate in the study. Among them, women who had previous history of psychiatric disorders (N=35), recurrence of cancer (N=34), or who were unable to give information and/or could not understand or read Bengali, the language spoken by the majority in this part of India (N=30) were excluded from the study, resulting in a total of 51 study participants.

On the basis of mechanism of action of chemo medicine, they were divided into two groups: group 1 (N=31) who got chemo medicine with combination of 5FU i.e. DNA modifying agent in conjugation with antimetabolite. Another one was group 2 (N= 20) who got chemo medicine with combination of other than 5FU i.e. metabolic inhibitor with DNA modifying agent. All the patients were given the cognitive function test by using validated tools: Kolkata Cognitive Battery. Inclusion and exclusion criteria are given below.

Following were the inclusion and exclusion criteria

Inclusion Criteria for Group 1 & 2

Age between 30 to 60 years

Diagnosed patients with early non metastatic breast cancer

Patients undergoing neo adjuvant chemotherapy

Willing to participate in the study

Minimum eight years of formal education

Exclusion Criteria

No history of past mental illness

Inability to understand or read Bengali language

Data Collection

Demographic data were collected from all the groups of the study population, followed by administration of tests in a single interview.

Instruments

Semistructured Proforma

A semi structured proforma was developed to record the sociodemographic and clinical details of the study subjects. Informed consent was obtained from all participants in writing according to the format laid down by the Indian Council for Medical Research (ICMR), the apex body governing research in India [8].

Kolkata Cognitive Battery(KCB)

Neurological assessment was conducted by using Kolkata Cognitive Battery.This battery consisted of category based on verbal fluency test, a 15 item version of the object naming test, mental status examination, calculation, word memory task, delayed word memory task, delayed word memory recognition task andvisual construction. This battery has already been used and validated by Syamal Kumar Das *et al.* the patients were affected by sever, moderate or slight cognitive impairment based on KCB scores [9].

Consent Form

Informed consent was obtained from all participants in writing according to the format laid down by the Indian Council for Medical Research (ICMR), the apex body governing research in India [8].

Procedure

Written informed consent was obtained from all participants. Study protocol was approved by Ethical Committee of institutions. Demographic data were collected via interview using the semistructured proforma. After dividing two groups by experienced oncologist, they were given the KCB.

Statistical Analysis

SPSS program version 21 was used for compilation and analysis of data. Descriptive statistics were calculated as the mean±standard deviation of age and frequency of demographic factors was tabulated according to relationship status, residence, education, occupation and per capita family income. The relationship between chemo-medicine and score of cognitive assessment was computed using the Spearman's rho correlation coefficient. Statistical significance was defined at $p<0.05$.

Results

Demographic Information

Table 1 shows the prevalence of cognitive function according to sociodemographic and clinicopathological factors

Table 1: *Prevalence of Cognitive function according to sociodemographic and clinicopathological factors*

Clinico Pathological factors	KCB (Mean±SE)	Sociodemographic Factors	KCB (Mean±SE)
Menopausal Status		**Age**	
Pre	33.64±5.85	26-35	35.25±9.28
Post	32.1±3.2	35-45	28.47±2.48
Tumour Grade		45-55	30.11±2.51
1	30.42±2.71	55+	28.31±1.89
2	29.42±1.79	**Marital Status**	
3	27.33±2.2	Living with spouse	28.61±2.19
Estrogen Receptor		Living without spouse	30.60±1.64
Positive	30.4±0.65	**Residence**	
Negative	31.5±2.1	Rural	27.8±1.63
Progesteron Receptor		urban	31.37±2.27
Positive	32.21±2.17	**Education**	
Negative	33.63±2.89	1-6 years	36.3±1.21
Her2/neu status		7-9 years	35.6±1.3
Over express	33.81±2.11	10-12 years	36.22±2.4
Not over express	30±2.52	Graduate or more	26.23±1.5
Number of chemotherapy			23.4±0.34
≤6th cycle	31.82±1.59	**Family Structure**	
More than 6th	28±1.5	Nuclear Family	30.94±2.91
Treatment Plan		Joint family	28.81±1.59
Neo-adjuvant chemotherapy	33.62±3.02	**Number of caregivers**	
Adjuvant chemotherapy	32.19±1.96	0	32.3±1.34
		1	31.34±2.1
		2	31.5±1.56
		3 or more	30±0.45
		Family income	
		<500	41.71±4.70
		500-1000	39.55±1.40

		1001-2000	37.36±2.59
		2000-3000	33.1±1.23
		>3000	32.09±1.41

While mentioning the demographic distribution of the studied patients, 47.5% among them were urban people while 52.5% were from rural areas. Age ranges were between 26 to over 55 yrs. Percentage of Patients were lowest (5%) among 26-35 yrs. and highest (42%) among 35-45 years. age group. Among studied patients 62% were living with their spouse and rest of part living alone. Highest percentage(62%) of patients were below high level of school educated. While mentioning cilinicopathological factors, it had been seen that, 58% of patients reported positive estrogen receptors while 53% of patients were with negative progesterone receptors. Human epidermal growth factor receptor 2 was expressed among 58% of patients. 63% of patients was diagnosed with ductal carcinoma. In case of treatment history, 69% of patients were undergoing neoadjuvant chemotherapy along with 61% patients already took more than 6th number of cycle chemotherapy.

In case of other medical illness, 47% of patients were with sugar. (Figure-1)

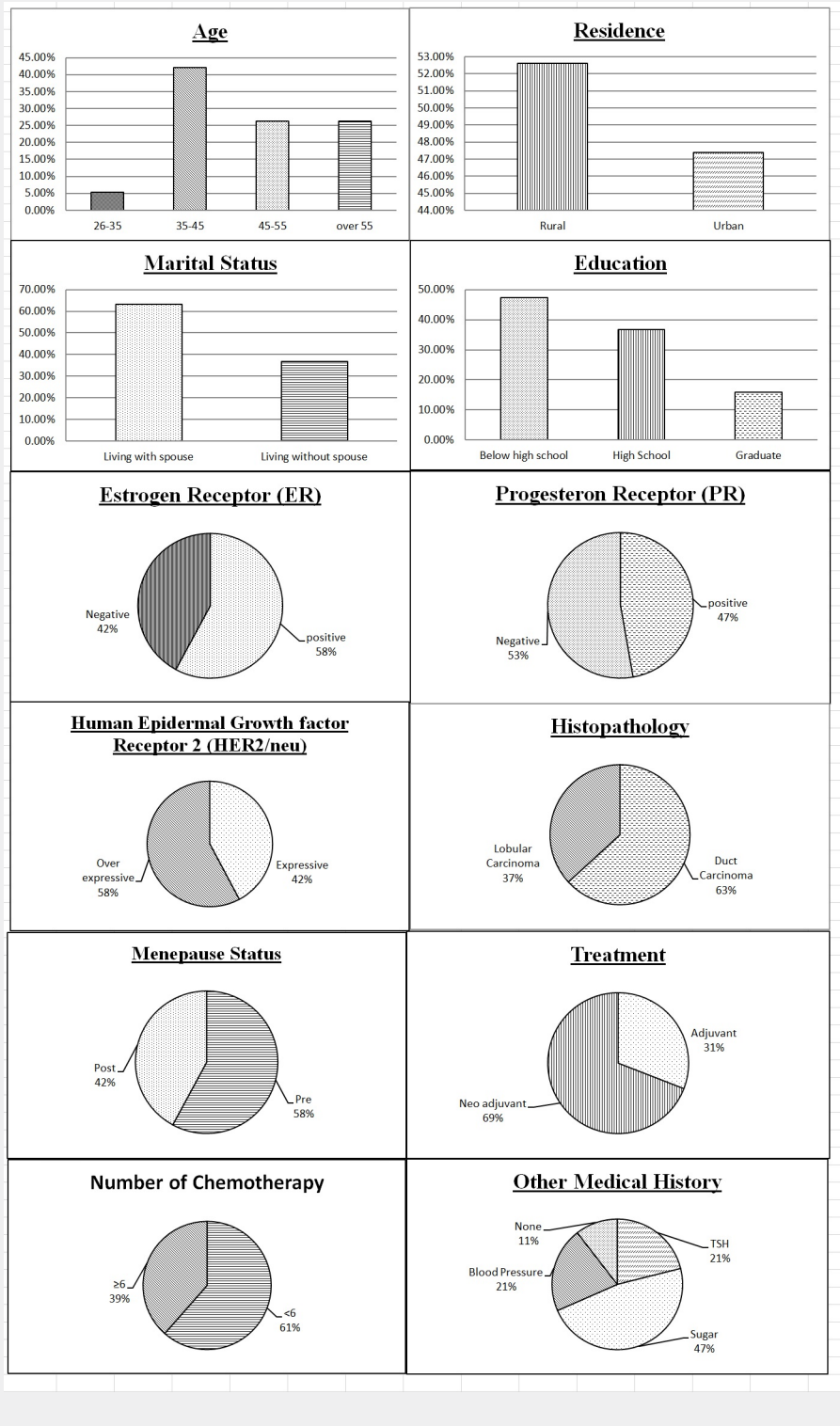
Age
45.00%
40.00%
35.00%
30.00%
25.00%
20.00%
15.00%
10.00%
5.00%
0.00%
26-35
35-45
45-55
over 55
Residence
53.00%
52.00%
51.00%
50.00%
49.00%
48.00%
47.00%
46.00%
45.00%
44.00%
Rural
Urban
Marital Status
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
Living with spouse
Living without spouse
Education
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
Below high school
High School
Graduate
Estrogen Receptor (ER)
Negative 42%
positive 58%
Progesteron Receptor (PR)
positive 47%
Negative 53%
Human Epidermal Growth factor Receptor 2 (HER2/neu)
Over expressive 58%
Expressive 42%
Histopathology
Lobular Carcinoma 37%
Duct Carcinoma 63%
Menepause Status
Post 42%
Pre 58%
Treatment
Adjuvant 31%
Neo adjuvant 69%
Number of Chemotherapy
≥6 39%
<6 61%
Other Medical History
None 11%
TSH 21%
Blood Pressure 21%
Sugar 47%

Figure 1

Table 1 showed prevalence of cognitive function according to sociodemographic and clinicopathological factors. Following the results of table, it had been seen, following clinic-pathological factors such as Menopausal status (pre and post), tumor grade (1,2, or 3), estrogen (positive or negative) & progesterone receptor status (positive or negative), Her2/neu status (positive and negative), type of treatment (adjuvant or neoadjuvant) was not significantly associated with cognitive function. While number of chemo cycle (≤6th cycle and More than 6th) was significantly associated with cognitive function.

According to results of table 1, it had been found, sociodemographic factors such as age, education, residency, family structure is not significantly associated with cognitive function. On the opposite side, family income variation was significantly associated with cognitive function.

Table 2 represents the prevalence of cognitive function according to different combination of chemo medicine. After going through, result had indicated, those patients were undergoing chemotherapy which was consist of 5FU combination medicine, they scored very low (specially, verbal fluency, delayed word memory recognition and word memory task) in the objective assessment rather than those took without combination of 5FU.

Table 2: *Prevalence of Cognitive function according to Chemo-medicine variation*

Chemo medicine	Verbal fluency	Object naming	MSE	Word memory	Word memory recognition	Delayed Word memory recognition	Vasoconstriction ability
With 5FU Combination							
Endoxan+adrim+5FU	8.7±2.1	10.7±1.4	11.7±1.2	1.9±0.6	1.6±0.00	1.96±0.2	5.08±0.05
Epirubicin+Endoxan+5FU	4.4±0.03	9.1±0.2	12.1±0.9	2.2±0.4	1.0±0.00	1.79±0.09	4.73±0.01
Paclitaxel+Cisplatin+5FU	3±1.2	6.1±0.5	19.6±2.7	2.3±0.3	1.7±0.07	1.54±0.05	6.1±0.04
MTX-+Docetaxel+adrim+-5FU	6.5±0.4	5.5±1.2	15.1±1.1	3.3±1.6	1.4±0.3	1.67±1.1	5.58±0.05
Without 5FU Combination							
Paclitaxel+Cisplatin+Endoxan	5±7.3	10.17±0.7	20.9±0.4	5.1±0.6	7.2±0.2	8.9±0.6	8.2±0.5
Gemictabine+Carboplatine	8±10.2	11.5±0.8	16±0.1	6.1±0.5	6.1±0.5	8.1±1.2	9.1±0.2
Cisplatine+Endoxan+Docetaxel	7±9.5	15±0.5	17±0.7	5.0±0.1	7.0±0.6	7.6±0.9	8.2±0.3

Table 3 represents effect of doses variation according to different combination of medicine. If focused on with combination of 5FU and its dosage variation it could be seen, verbal fluency (1.4(.99-1.81), object naming [1.94(1.81-2.06)], word memory task [.1(.11-10.99)], delayed word memory recognition [.25(.17-3.49)*] and visuo-construction ability [.51(.39-7.15)*] is significantly associated with dosages variation.

Table 3: *Prevalence of cognitive function according to doses variation of chemo-medicine*

	Dosages Variation	
Cognitive Domains	**Combination with 5FU**	**Combination without 5FU**
Verbal Fluency	1.4(.99-1.81)*	1.13(2.07-2.45)*
Object Naming	1.94(1.81-2.06)*	2.26(2.04-2.44)*
MSE	2.92(2.75-3.09)	1.14(1.36-1.65)
Word Memory task Trai-1 Trail-2 Trail-3	.1(.11-10.99)* .28(.13-4.49)* 1.61(0.58-2.21)	0.99(0.00-1) 0.5(0.00-1) 0.73(0.37-1.51)
Delayed Word Memory	.94(.03-4.8)	3.11(.00-.49)*
Delayed Word recognition	.25(.17-3.49)*	1.7(.02-1.83)*
Visu Construction ability	.51(.39-7.15)*	1.54(.05-.89)

In combination without 5FU, there dosages variation significantly associated with verbal fluency [1.13(2.07-2.45)*], objection naming [2.26(2.04-2.44)*], word memory recognition [3.11(.00-.49)*] and delayed word memory recognition [1.7(.02-1.83)*].

Table 4 represents effects of 5FU on cognitive function.

Table 4: *Prevalence of cognitive function according to doses variation of chemo-medicine*

Cognitive Domains	**Combination with 5FU**	**Combination without 5FU**
Verbal Fluency	1.8(1.323-2.27)*	1.14(2.85-3.05)*
Object Naming	2.64(2.24-3.05)*	2(1.58-3.41)*
MSE	1.2(1.4-1.98)*	2.5(2.06-2.46)*
Word Memory task Trail-1 Trail-2 Trail-3	2.5(1.50-3.5) 2.72(2.6-3.31) 2.96(2.42-3.2)	1.01(1.41-1.69) 1.5(1.33-1.67) 1.79(0.02-1.24)
Delayed Word Memory	2.72(2.6-3.31)	5.04(.00-.12)
Delayed Word recognition	2.96(2.24-3.2)	1.89(.01-1.84)
Visu Construction ability	1.19(1.34-1.63)*	1.1(.03-3.72)

Chemo medicine combination With 5FU

Medicine: chemocycle, verbal fluency and time, calculation, word memory Trail 1 and Trail 2 was significantly correlated with variation in chemo medicine.

Chemo medicine combination Without 5FU

Medicine: chemocycle, verbal fluency, Object naming and time, MSE.

Discussion

The present studies that only address cognitive performance in a cross-sectional manner on the basis of impact of different chemo-medicine on cognitive function. Possible difference had been determined on the basis of effect of DNA mechanism of combination of each medicine. To get around these limitations of the patients' investigation, investigators have begun to conduct studies that perform assessment of cognitive functionamong mentioned two groups. The result of present study had reported, in initial condition during period of chemotherapy, impairment in cognitive function was not significantly affected. In some of longitudinal studies had reported some of cognitive impairment such as memory, executive function after following their treatment but in short -term case of treatment did not find cognitive changes [10]. Chemotherapy related cognitive changes is known adverse effect among breast cancer those who are under chemotherapy. Unfortunately, this type of cognitive complained was not clinically proved. Similarly, some of researchers had worked over women breast cancer patients who were receiving adjuvant and neoadjuvant chemotherapy. The authors ultimately found that a patient's anxiety, depression and low mood is significantly associated with subjective cognitive function but it was not elicited in neurological assessment [11]. Endocrine factors may influence objective neurological testing performance after chemotherapy [12]. In a longitudinal study of breast cancer patients undergoing chemotherapy for early breast cancer patients, menopause was associated with some decline in cognitive performance following chemotherapy and it was proved in neurological assessment (Tager FA *et al.* 2010). This result was contradicted with another prospective study of women receiving adjuvant chemotherapy. In their study, they had predicted, menopausal symptoms correlated with quality of life scores but not cognitive performance, as it was determined by high-sensitivity cognitive screen [13].

Apart from this, objective study is supported with Jonna. E. Fardell (2012) [14] research entitled : "cognitive impairment caused by oxiliplantin and 5- fluorouracil chemotherapy are ameliorated by physical activity". Studies in women with breast cancer have demonstrated that chemotherapy can have a negative impact on cognitive performance. The results of the present study reported, 5- fluorouracil (5FU) chemotherapy agents had created a negative impact on memory, verbal fluency and calculation. This result is supported with Jenna E (2012) [15]. But, it had been seen, scores of verbal fluency was low in both case those who receive chemotherapy with combination of 5FU regimens and those who not.

The hypothesis of a dosage response relationship between chemotherapy and cognitive impairment in breast cancer patients was confirmed by Collins *et al* [16]. after controlling baseline performance along with a patient's age, education mood they found that cognitive function rapidly worsens with cumulative chemotherapy.

Our study had contradicted with Giffard *et al* [17]. reported that because of life threatening cancer and its treatment both also may involve many stressful events and suffering from psychiatric symptoms such as PTSD, anxiety and depression. These symptoms are known to effect on cognition. A relationship between hypocampal atrophy and deficit in episodic autobiographical memory retrieval was suggested which could reflect of exposure to negative events with cumulative stress.

Chemotherapy can improve prospects for long-term survival after a cancer diagnosis, but it turns survival after a cancer diagnosis, but it may also be associated with long-term toxicity including possibility of cognitive dysfunction. Pharmacologic treatments do not have related cognitive function, clinical guidelines are needed for assessment and management of chemotherapy related cognitive dysfunction.

Therefore, from this study it has been suggested in many cases, chemotherapy medicines are given in combination which means a patient gets two or more than two medicine at the same time which is known as chemotherapy regimens. So, dependency on regimens is not only individual cause of cognitive impairment.

Conclusion

In the present study we have investigated correlated factors for cognitive impairment, comorbidity factors of the two conditions and it had found there sociodemographic as well as clinical factors were similar among the three conditions through an exploratory way. Among the correlated factors, in case of dempgraphic and clinical factor was not associated with cognitive dysfunction. Considering the moderate level of decline and increased risk factor adverse outcome among those with cognitive impairment, it could better be suggested that patients with evaluated a proper psychological intervention to give a better quality of life.

Limitations of the Study

This study has its limitations. It was conducted on a relatively small sample size. Most patients belonged to lower socioeconomic strata and had lesser number of years in terms of formal education, hence it cannot be said to be representative of all Indian women. No follow up was carried out except for a single sitting with breast cancer patients to look into their major concerns of life. Finally, we did not look into the possible protective factors against depression, and more specifically, impaired cognitive performance in cancer patients. We hope to address these issues in future studies.

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