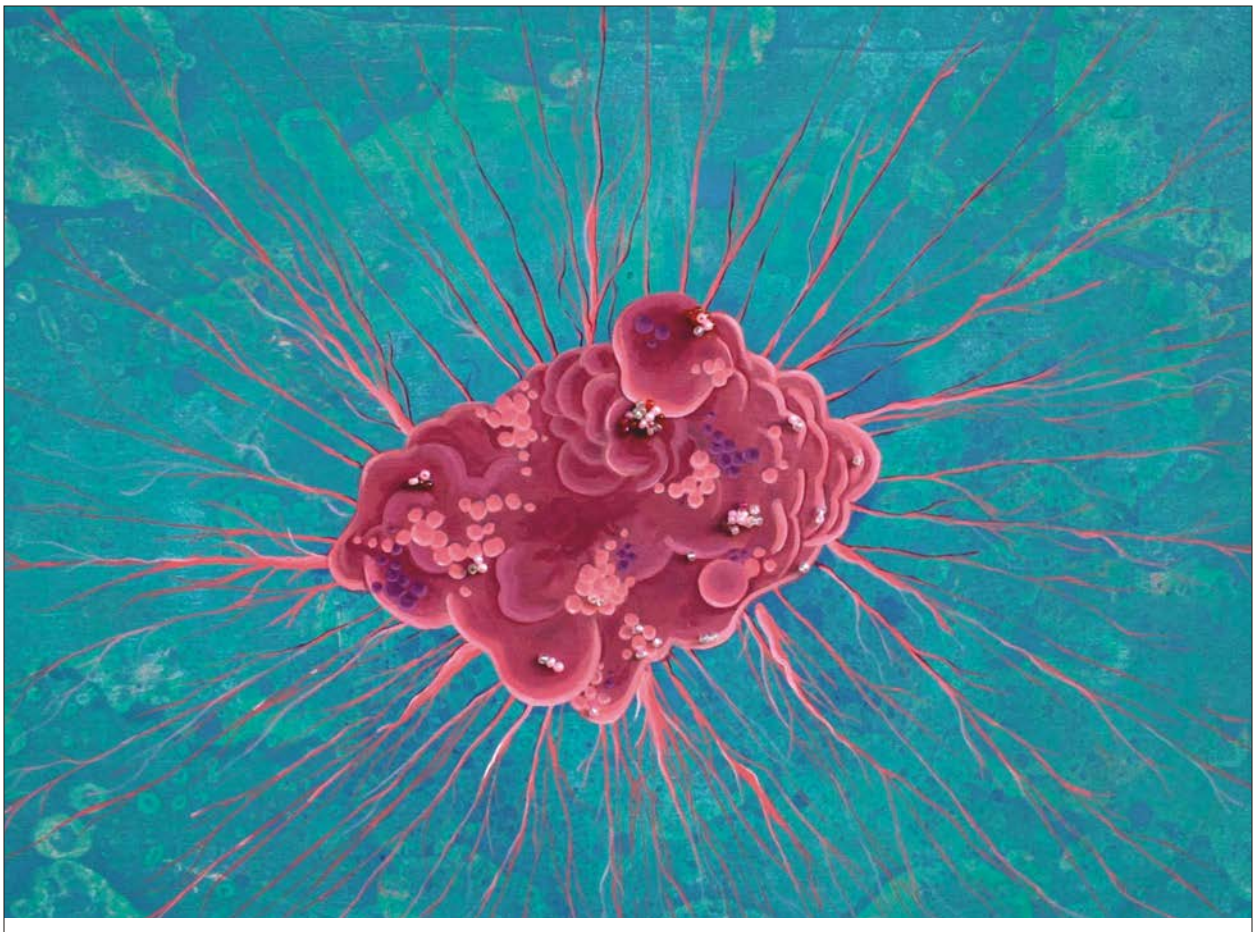

International Journal of Cancer Research

ISSN 1811-9727

Academic Journals Inc.

www.academicjournals.com

OPEN ACCESS International Journal of Cancer Research

ISSN 1811-9727
DOI: 10.3923/ijcr.2018.52.57

Systematic Review
Effect of Cancer Chemotherapy on Cognitive Function

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Abstract

Background and Objective: Cognitive dysfunction is one of the mental disorders and defined as the impairment in the process of understanding such as knowledge, memory power, attention, analysis, judgment and problem solving etc. Cognitive impairment due to chemotherapy has been reported in 17-75% of patients. Cognitive function can be measured by different subjective and objective assessment techniques. The idea of this systematic review was to appraise the recently published evidence on effect of cancer chemotherapy on cognitive function. The study was designed to evaluate the effect of cancer chemotherapy on cognitive function. **Methodology:** A comprehensive literature search of articles on the assessment of the effect of cancer chemotherapy on cognitive function was carried out. Based on selection criteria of the study, the articles were reviewed. Cognitive function assessment methods used were different in each of the study article. **Results:** This review conveyed that the positive correlation between cancer chemotherapeutic regimens and decline in the level of cognitive functioning. It brings out the fact that mechanisms like oxidative stress induced by treatment characteristics like dosage, duration, type of regimen, genetic factors such as ApoE4, COMT-Val, imbalance in cytokines like IL-6,TNF-alpha, IL-1 beta which act as mediating factors for CNS damage, leads to cognitive dysfunction. Patients with any type of cancer, treated with chemotherapy drugs experience a considerable decline in level of cognitive function. **Conclusion:** Patients with any type of cancer, treated with chemotherapy drugs experience a considerable decline in level of cognitive function.

Key words: Cognitive dysfunction, ApoE4, COMT-Val, chemotherapy, cytokines

Citation: Divya Krupa Muniyandi, Rajanandh Muhasaparur Ganesan, Manichavasagam Meenakshisundaram and Seenivasan Palanichamy, 2018. Effect of cancer chemotherapy on cognitive function. Int. J. Cancer Res., 14: 52-57.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

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, anemia, liver disease etc, alterations in hormonal levels like deprivation of androgen and estrogen, genetic factors such as Apolipoprotein E(ApoE), Catechol-O-Methyltransferase (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 chemo therapy and so the term chemo brain. 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. The COMT plays a role in the breakdown of catecholamines[12-14].

Cognitive impairment due to chemotherapy has been reported in 17-75% 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. In order to get a clarity on these differences of opinion, the present review was carried out.

MATERIALS AND METHODS

A comprehensive literature search of articles on the assessment of the effect of cancer chemotherapy on cognitive function was carried out. Selection criteria for articles in this review was as follows: Articles published within last 10 years (2007-2017), study should have more than 30 participants, adults not less than 18 years, both genders, patients diagnosed with any type of cancer and on concurrent chemotherapy regimens for a period of at least 3 months.

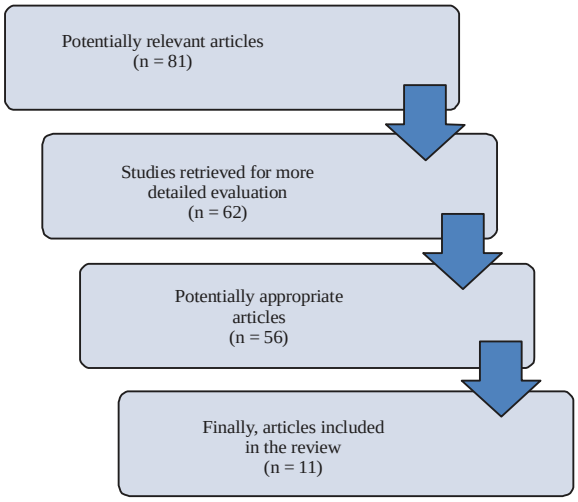

Fig. 1: Systematic review protocol

The search was narrowed down to original research articles. Studies which included brain metastasis, reviews, case reports, studies in special population and patients with co-morbidities were excluded. The search was restricted to articles published in English. Of the 56 appropriate articles collected, 11 articles were included based on the inclusion criteria. The systematic review protocol was represented in Fig. 1.

The study characteristics such as name of the author(s), year of publication, number of patients, study type, type of cancer, nature of chemotherapy, method of cognitive function assessment such as questionnaire type (subjective assessment) or measurement of any blood marker (objective assessment), health related quality of life, disease duration and the outcome measures were noted and checked.

RESULTS AND DISCUSSION

The effect of cancer chemotherapy on cognitive function was addressed by 11 studies of which 4 were multi-center longitudinal, 3 were case-control, 1 cohort and 3 prospective longitudinal studies (Table 1). The outcome of various studies selected for the review was portrayed in Table 2.

A prospective cohort study conducted by Ramalho *et al.*[16] on 418 patients with breast cancer on doxorubicin+ cyclophosphamide, doxorubicin+cyclophosphamide+ docetaxel, 5-Fluorouracil+epirubicin+cyclophosphamide,

Table 1: Studies reporting the different tools used in assessing cognitive function in cancer patients

Name of the authors	Year	Number of patients	Study type	Type of cancer	Chemotherapy regimen	Tools used: Questionnaire	Tools used: Blood marker	Tools used: Others
Cerulla N *et al.*[18]	2017	51	Prospective longitudinal study	CA breast	Fluorouracil, epirubicin and cyclophosphamide, taxanes	Mood, anxiety and fatigue questionnaires	---	Neuropsy-chological tests
Hermelink K *et al.*[24]	2007	101	Multicentre prospective longitudinal	CA breast	Epirubicin, paclitaxel and cyclophosphamide, darbepoetin α	Questionnaire of experienced attention deficits (FEDA), cognitive function scale of EORTC QoL Ques.C30, HADS	---	Neuropsy-chological tests
Janelsins MC *et al.*[17]	2017	581-364	Multicentre prospective longitudinal	CA breast	Anthracycline and non-anthracyclines	FACT-Cog version 2, WRAT-4 reading subscale, Spielberger State/Trait anxiety inventory state score (form Y-1), Multidimensional fatigue symptom inventory	---	---
Jim HSL *et al.*[23]	2009	187-187	Case-control	CA breast	Not mentioned	MAQ	---	NART, CVLT, Trails A subtest of the trail making test, visual reproduction subtest of the WMS-III, Digit symbol subtest of the WAIS-III
Kohli S *et al.*[25]	2007	595	Multicentre longitudinal study	CA breast, lung, prostate, hematologic, gastrointestinal, or head and neck	Not mentioned	Karnofsky performance status, The symptom inventory	---	---
Ng R *et al.*[19]	2016	146	Multicentre longitudinal	CA breast-early stage	Anthracycline and taxane	FACT-Cog and headminder	VEGF	---
Ramalho M *et al.*[16]	2017	418	Prospective cohort	CA breast	Doxorubicin+cyclophosphamide, doxorubicin+cyclophosphamide+ docetaxel, 5-Fluorouracil+epirubicin+ cyclophosphamide, 5-Fluorouracil+ epirubicin+cyclophosphamide+ docetaxel, others	HADS and MoCA	---	---
Sequeira AZ *et al.*[20]	2014	30-30	Cross sectional case-control	CA breast	Not mentioned	SMMSE, TMT-B and DSST	---	---
Stewart A *et al.*[26]	2008	61-51	Prospective case-control study	CA breast	Adjuvant chemotherapy and hormonal therapy	---	---	Neuropsychological testing and mood rating scale
Vardy J *et al.*[21]	2014	291-72-72	Prospective longitudinal study	Localised CRC (group 1)-limited metastatic or locally recurrent CRC (group 2) before chemotherapy-Healthy controls	Not mentioned	CANTAB, Modified six elements test, FACT-cog version 2, FACT-G, FACT-fatigue (F), GHQ	Carcinoembryonic antigen, Tumour-necrosis factor-α	Neuropsychological tests
Wefel JS *et al.*[22]	2010	42	Prospective longitudinal randomized phase 3 treatment trial	T1-3, N0-1, M0 breast cancer	5-fluorouracil, doxorubicin and cyclophosphamide with or without paclitaxel	FACT-Breast module	---	Neuropsychological tests and mood measures

HADS: Hospital anxiety and depression scale, WAIS-III: Weschler administration and scoring manual, WRAT-4: Wide range achievement test, 4th edition, FACT-Cog: Functional assessment of cancer therapy- cognitive function, MAQ: Mental abilities questionnaire, VEGF: Vascular endothelial growth factor, NART: National adult reading test, MoCA: Montreal Cognitive assessment, CVLT: California verbal learning test, SMMSE: Standardized mini-mental state examination, WMS-II: Weschler memory scales-III, TMT-B: Trail-making test B, DSST: Digit symbol substitution test, CANTAB: Cambridge neuropsychological test automated battery, GHQ: General health questionnaire

Table 2: Study outcome of various studies selected for the review

Name of the authors	Study outcome
Cerulla N *et al.*[18]	Chemotherapy for BC with a FEC regimen can have a negative effect on cognition. Acute deficits seem to be larger when taxanes are added but treatment seems to affect cognition also at long term
Hermelink K *et al.*[24]	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
Janelsins MC *et al.*[17]	Self-reported cognitive decline among patients with breast cancer was 36.5% from prechemotherapy to 6 months after chemotherapy completion (11.5 months from prechemotherapy)
Jim HSL *et al.*[23]	Cognitive deficits noted in breast cancer survivors are relatively subtle and are the result of the general effects of cancer rather than systemic treatment
Kohli S *et al.*[25]	Cognitive impairment is a debilitating and prevalent adverse effect and cognitive problems are associated with cancer and its treatment
Ng R *et al.*[19]	VEGF levels are dysregulated during chemotherapy but are not associated with cognitive impairment
Ramalho M *et al.*[16]	Cognitive function is affected due to chemotherapy but only among women with no anxiety at baseline
Sequeira AZ *et al.*[20]	Breast cancer patients show statistically significant cognitive deficits as compared to non cancer individuals
Stewart A *et al.*[26]	A 3 fold greater risk of cognitive decline was found in the chemotherapy patients compared to the hormonal patients
Vardy J *et al.*[21]	Almost half of CRC patients have cognitive impairment and a similar proportion report fatigue at or soon after diagnosis and these rates are significantly higher than in controls. Women had greater rates of cognitive impairment than men
Wefel JS *et al.*[22]	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

BC: Breast cancer, FEC: 5-Fluorouracil, epirubicin, cyclophosphamide, CRC: Colorectal cancer

5-Fluorouracil+epirubicin+cyclophosphamide+docetaxel regimens using hospital anxiety and depression scale and MoCA showed that cognitive function was affected in women with breast cancer for 1 year. But cognitive decline was found only among women with no anxiety at baseline in this study.

A large multi-center prospective longitudinal case-control study conducted by Janelsins *et al.*[17] on 581 breast cancer patients on anthracycline or non-anthracycline containing regimens and 364 non-cancer controls using FACT-Cog version 2, Spielberger state/Trait anxiety inventory state score (form Y-1), wide range achievement test, 4th edition reading subscale (WRAT-4), multidimensional fatigue symptom inventory showed that cognitive decline among breast cancer patients was 36.5% from pre-chemotherapy to 6 months after chemotherapy completion.

Another prospective longitudinal study by Cerulla *et al.*[18] on 51 breast cancer patients on treatment with a fluorouracil, epirubicin and cyclophosphamide (FEC) regimen alone or along with taxanes were compared at 3 moments; before chemo, after its completion and at a mean of 74.5 weeks from baseline as long term evaluation. The study revealed that chemotherapy for breast cancer with a FEC regimen can have a negative effect on cognition.

Ng *et al.*[19] had conducted a multicentre longitudinal study in 2016 on 146 breast cancer patients diagnosed with early stage disease. The patients were on anthracycline or taxane chemotherapy regimen. Plasma vascular endothelial growth factor (VEGF) level was measured. The cognitive function assessment tools used were functional assessment of cancer therapy-cognitive function (FACT-Cog) and headminder. The outcome of the study was that VEGF levels were dysregulated during chemotherapy but were not associated with cognitive impairment.

Sequeira and Krishnamurthy[20] had conducted a cross-sectional case-control study on 30 breast cancer patients and 30 non cancer controls in 2014 using standardized mini mental status examination (SMMSE), Trail making test B (TMT-B) and digit symbol substitution test (DSST). The study revealed that breast cancer patients showed statistically significant cognitive deficits as compared to non cancer individuals.

Vardy *et al.*[21] 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 *et al.*[22] 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 *et al.*[23] 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 Weschler 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 *et al.*[24] 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 patient's 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 *et al.*[25] 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 and cognitive problems are associated with cancer and its treatment.

A prospective case-control study was conducted by Stewart *et al.*[26] on breast cancer patients. The study enrolled 61 breast cancer patients on adjuvant chemotherapy and a control group of 51 womens 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[27,28].

CONCLUSION

This review conveys a positive correlation between cancer chemotherapeutic regimens and decline in the level of cognitive functioning. It brings out the fact that mechanisms like oxidative stress induced by treatment characteristics like dosage, duration, type of regimen, genetic factors like ApoE4, COMT-Val, etc., imbalance in cytokines like IL-6,TNF-alpha, IL-1 beta which act as mediating factors for CNS damage which leads to cognitive dysfunction, hormonal factors like oestrogen, progesterone cause telomere shortening leading to the primary outcome of CNS damage which results in chemo brain which reduces the quality of life of cancer patients. Patients with any type of cancer, treated with chemotherapy drugs experience a substantial decline in level of cognitive function.

SIGNIFICANCE STATEMENT

This study identified a significant correlation between cancer chemotherapeutic regimens and decline in the level of cognitive functioning. The findings of this study will be helpful to healthcare professionals especially to oncologists to in choosing the chemotherapeutic drug regimen.

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