Cancer Association of South Africa (CANSA)

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Fact Sheet on Chemo Brain

Introduction

Chemo brain, also known as post-chemotherapy cognitive impairment (PCCI), chemotherapy-induced cognitive dysfunction or impairment, or chemo fog, describes the cognitive impairment that can result from chemotherapy treatment. Approximately 20–30% of people who undergo chemotherapy experience some level of post-chemotherapy cognitive impairment. The phenomenon first came to light because of the large number of breast cancer survivors who complained of changes in memory, fluency, and other cognitive abilities that impeded their ability to function as they had pre-chemotherapy.

[Picture Credit: Chemo Brain]

Although the causes and existence of post-chemotherapy cognitive impairment has been a subject of debate, recent studies have confirmed that post-chemotherapy cognitive impairment is a real, measurable side effect of chemotherapy that appears in some patients. While any cancer patient may experience temporary cognitive impairment while undergoing chemotherapy, patients with PCCI continue to experience these symptoms long after chemotherapy has been completed. PCCI is often seen in patients treated for breast cancer, ovarian cancer, prostate cancer, and other reproductive cancers, as well as other types of cancers requiring aggressive treatment with chemotherapy.

The clinical relevance of PCCI is significant, considering the increasing number of long-term cancer survivors in the population, many of whom may have been treated with aggressive dosing of chemotherapeutic agents, or with chemotherapy as an adjuvant to other forms of treatment. In some patients, fear of PCCI can impact treatment decisions. The magnitude of chemotherapy-related cognitive changes and their impact on the activities of daily living are uncertain.

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Sordillo, P.P. & Sordillo, L.A. 2020.
"The majority of patients receiving chemotherapy experience post-chemotherapy cognitive impairment, sometimes referred to as "chemo brain" or "chemo fog." The cognitive impairment associated with this syndrome can be severe, and can sometimes last for many years after therapy discontinuation. Despite extensive investigations, its etiology is unknown. We argue that chemo brain results from damage to tubulin within microtubules. This damage can occur directly from tubulin inhibitors such as taxanes, epothilones or vinca alkaloids. Other chemotherapies stimulate increased mitochondrial activity and biophoton release. This results in abnormal tryptophan metabolism and excess production of neurotoxic kynurenines, which, in turn, damage microtubules."

Post-chemotherapy Cognitive Impairment (PCCI)
Chemo brain is a common term used by cancer survivors to describe thinking and memory problems that can occur after cancer treatment. Chemo brain can also be called chemo fog, chemotherapy-related cognitive impairment or cognitive dysfunction.

Though chemo brain is a widely used term, it's misleading. It's unlikely that chemotherapy is the sole cause of concentration and memory problems in cancer survivors. Despite the many questions with regard to this problem, it is clear that the memory problems commonly called chemo brain can be a frustrating and debilitating side effect of cancer and its treatment. More study is needed to understand this condition.

Cancer patients have long complained of neurological side effects such as short-term memory loss and, in extreme cases, seizures, vision loss, and even dementia. Until very recently, these cognitive side effects were often dismissed as the by-product of fatigue, depression, and anxiety related to cancer diagnosis and treatment. Now a growing body of evidence has documented the scope of these conditions, collectively referred to as chemo brain. And while it is increasingly acknowledged by the scientific community that many chemotherapy agents may have a negative impact on brain function in a subset of cancer patients, the precise mechanisms that underlie this dysfunction have not been identified.

Virtually all cancer survivors experience short-term memory loss and difficulty concentrating during and shortly after treatment. A study two years ago by researchers with the James P. Wilmot Cancer Center at the University of Rochester showed that upwards of 82% of breast cancer patients reported that they suffer from some form of cognitive impairment.

[Picture Credit: Blame it on Chemo Brain]

While these effects tend to wear off over time, a subset of patients, particularly those who have been administered high doses of chemotherapy, begin to experience these cognitive side effects months or longer after treatment has ceased and the drugs have long since departed their systems. For example, a recent study estimates that somewhere between 15 and 20 percent of the nation's 2.4 million female breast cancer survivors have lingering cognitive problems years after treatment. Another study showed that 50 percent of women had not recovered their previous level of cognitive function one year after treatment.

Eide, S. & Feng, Z-P. 2020.
"Doxorubicin is a leading chemotherapeutic halting cellular replication and inducing p53-dependent apoptosis in cancerous tissue. Like many chemotherapies, doxorubicin damages healthy tissue throughout the body through cellular mechanisms independent of its chemotherapeutic action. Although cognitive impairment is commonly recorded in patients after chemotherapy, the occurrence of doxorubicin-induced "chemo-brain" is debated, as doxorubicin cannot cross the blood-brain barrier. However, the potential of indirect doxorubicin neurotoxicity remains, providing a foundation for doxorubicin-mediated chemo-brain. We present the first meta-analysis of defined cognitive performance of doxorubicin-treated patients. A search of PubMed and MedLine collected 494 studies, 14 of which met analysis criteria. Performance of 511 doxorubicin-treated women with breast cancer was compared to that of 306 healthy controls across measures of defined cognitive modalities. Treated patients experience significant impairment in global cognition compared to controls ($g_{=}$ -0.41, $P < 0.001$), with select impairment in executive function ($g = -0.25$, $P < 0.0001$), language ($g = -0.30$, $P < 0.0001$), memory ($g = -0.12$, $P < 0.01$) and processing speed ($g = -0.28$, $P < 0.01$). Within memory, short-term verbal memory is most significantly affected ($g = -0.21$, $P < 0.01$). Impairment in select cognitive modalities (executive function, language, memory, short-term verbal memory, processing speed) is prevalent in doxorubicin-treated patients, with some cognitive functions remaining intact (attention, motor function, visuospatial abilities). This information can guide the development of future interventions to improve quality-of-life (QOL) and doxorubicin-derived therapies that target cytotoxicity to cancerous tissue, avoiding healthy tissue damage, which is mediated by seemingly independent mechanisms."

Regier, N.G., Naik, A.D., Mulligan, E.A., Nasreddine, Z.S., Driver, J.A., Sada, Y.H. & Moye, J. 2019.
OBJECTIVE: This study examines the demographic and clinical variables associated with cancer-related cognitive impairment (CRCI) in a sample of older, male, oral-digestive cancer survivors at VA Medical Centers in Boston and Houston.
METHODS: A two-time point, longitudinal design was used, with cognitive assessment conducted at 6 and 18 months post-diagnosis. Using ANCOVA, the cognitive functioning of 88 older adults with head and neck, esophageal, gastric, or colorectal cancers was compared with that of 88 healthy controls. Paired t-tests examined cognitive change over time in the cancer group. Hierarchical linear regression examined variables potentially associated with cognitive impairment at 18 months.
RESULTS: Forty-eight percent of cancer patients exhibited cognitive impairment 6 months post-cancer diagnosis, and 40% at 18 months. Cancer survivors were impaired relative to controls on measures of sustained attention, memory, and verbal fluency at 18 months, controlling for age. Older age, low hemoglobin, and cancer-related PTSD were associated with worse cognition at 18 months.
CONCLUSIONS: CRCI is more frequent in older adults than reported in studies of younger adults and may be more frequent in men. Potential areas of intervention for CRCI include psychotherapy for cancer-related PTSD, treatment of anemia, and awareness of particularly vulnerable cognitive domains such as sustained attention, memory, and verbal fluency.

Causes of Post-chemotherapy Cognitive Impairment (PCCI)
It is still not clear what causes mild cognitive impairment.

Olson, B. & Marks, D.L. 2019. "Cognitive changes are common in patients with active cancer and during its remission. This has largely been blamed on therapy-related toxicities and diagnosis-related stress, with little attention paid to the biological impact of cancer itself. A plethora of clinical studies demonstrates that cancer patients experience cognitive impairment during and after treatment.

However, recent studies show that a significant portion of patients with non-central nervous system (CNS) tumors experience cognitive decline *prior* to treatment, suggesting a role for tumor-derived factors in modulating cognition and behavior. Cancer-related cognitive impairment (CRCI) negatively impacts a patient's quality of life, reduces occupational and social functioning, and increases morbidity and mortality. Furthermore, patients with cancer cachexia frequently experience a stark neurocognitive decline, suggesting peripheral tumors exert an enduring toll on the brain during this chronic paraneoplastic syndrome. However, the scarcity of research on cognitive impairment in non-CNS cancers makes it difficult to isolate psychosocial, genetic, behavioral, and pathophysiological factors in CRCI. Furthermore, clinical models of CRCI are frequently confounded by complicated drug regimens that inherently affect neurocognitive processes. The severity of CRCI varies considerably amongst patients and highlights its multifactorial nature. Untangling the biological aspects of CRCI from genetic, psychosocial, and behavioral factors is non-trivial, yet vital in understanding the pathogenesis of CRCI and discovering means for therapeutic intervention. Recent evidence demonstrating the ability of peripheral tumors to alter CNS pathways in murine models is compelling, and it allows researchers to isolate the underlying biological mechanisms from the confounding psychosocial stressors found in the clinic. This review summarizes the state of the science of CRCI independent of treatment and focuses on biological mechanisms in which peripheral cancers modulate the CNS."

Research suggests that there may be a number of factors that contribute to it, including:

Chemotherapy - so far, research has not clearly shown whether chemotherapy causes these thought and memory changes. Early studies only tested people after their chemotherapy. These tests showed that people had cognitive impairment. But more recent research has shown that some people with cancer have similar problems before they start any treatment and that the changes may even improve during treatment. This implies that it could be something to do with having cancer, rather than having cancer treatment. There are, however, many individuals complaining of post-chemotherapy cognitive impairment who are certain that they never had similar problems before their cancer treatment.

Other cancer treatments - many people have more than one type of treatment for cancer, which makes it difficult to work out what is causing a particular side effect. A small study looked at 31 women treated with the hormone therapies, tamoxifen and anastrozole. They found that women taking anastrozole had more thought and memory problems than women taking tamoxifen. Another study compared women taking tamoxifen with women taking exemestane and with women who had not had breast cancer. This study found that the women taking tamoxifen had more problems with memory and organisation skills than those taking exemestane and the women who hadn't had cancer. We need more research to find out what effects hormone therapy and other cancer treatments may have.

Anxiety, fatigue, old age, depression - from research, we know that people who report thought and memory problems after chemo are more likely to have anxiety and depression than people who don't have these symptoms. But it isn't clear whether one causes the other. There could be another factor that leads to thought and memory problems as well as anxiety and depression.

Changes in blood proteins called cytokines - Cytokines are proteins made by the body as part of the immune response. Researchers have looked at blood levels of cytokines in women who had treatment for breast cancer. The researchers compared them with cytokine levels in women who didn't have breast cancer. They found that women with breast cancer had higher cytokine levels. They also found that women who reported thought and memory problems had the highest levels of cytokines. We need more research to find out what this actually means. The researchers are extending their study to include more women who have had breast cancer and also people with other types of cancer.

Signs and Symptoms of Post-chemotherapy Cognitive Impairment (PCCI)

Any person who has received cancer treatment and are experiencing the following types of problems, may be experiencing PCCI:

- Memory loss
- Trouble paying attention
- Short attention span
- Fumbling for the right word or phrase
- Difficulty with new learning
- Difficulty managing daily activities
- Difficulty concentrating on a single task
- Difficulty learning new skills
- Problems with short-term memory; forgetting details of recent events
- Feeling mentally 'slower' than usual
- Confusing dates and appointments
- Misplacing objects
- Being unusually disorganised
- Difficulty concentrating
- Difficulty multitasking
- Taking longer than usual to complete routine tasks
- Trouble with verbal memory, such as remembering a conversation
- Trouble with visual memory, such as recalling an image or list of words

People often notice these problems during chemotherapy treatment. Within one year of treatment, many people find these difficulties greatly improve or no longer exist. However, for some people, PCCI can continue for years following completion of treatment.

Preventing and Treating Post-chemotherapy Cognitive Impairment (PCCI)

Doctors have been looking into how to prevent and treat cancer related thought and memory problems. It is still too early to know how well these work but they include:

- Erythropoietin (EPO)) – this drug may help by raising haemoglobin levels
- Aspirin – which works as a mild blood thinning drug
- Methylphenidate – a type of stimulant for chronic fatigue syndrome, daytime drowsiness and attention deficit disorder

The aim with EPO or aspirin treatment is to maintain or increase blood flow to the brain cells and so increase their oxygen supply. Understanding more about what causes PCCI will help doctors to find ways of preventing and treating it.

Srivastrava, R.K. & Singh, P. 2020.
"Chemo brain, a constellation of cognitive deficiencies followed by chemotherapy drugs, used to treat different types of cancers and adversely impacts the quality of life of a cancer survivor. The underlying mechanism of chemo brain remains vague, thus delaying the advancement of efficient treatments. Unfortunately, there is no US FDA approved medicine for chemo brain and often medicines considered for chemo brain are already the ones approved for other diseases. Nevertheless, researches exploring stem cell transplantation in different neurodegenerative diseases demonstrate that cellular transplantation could reverse chemotherapy-induced chemo brain. This review talks about the mechanism behind the cognitive impairments instigated by different chemotherapy drugs used in cancer treatment, and how stem cell therapy could be advantageous to overcome this disease."

Salerno, E.A., Rowland, K., Kramer, A.F. & McAuley, E. 2019.
BACKGROUND: Many breast cancer survivors (BCS) report deficits in cognitive function. Physical activity (PA) has been associated with better processing speed and memory in healthy adults and thus may be a useful method for improving cognition in BCS. The purpose of this study was to examine the effects of an acute bout of PA on processing speed and spatial working memory in a sample of BCS.
METHODS: Using a repeated measures, crossover design, BCS [N = 27; M_{age} (SD) = 49.11(8.05)] completed two sessions in counterbalanced order: 30 min of moderate-intensity treadmill walking and 30 min of seated rest. Women completed cognitive tasks immediately before and after each session.
RESULTS: Within-subjects repeated measures analyses of variance revealed a significant time by session effect for processing speed reaction time [F (1,25) = 5.02, p = .03, η2 = 0.17]. This interaction was driven by significantly reduced reaction time (e.g., faster response) post-exercise and no change post-rest. Further between-subjects analyses indicated a significant time by session by moderate to vigorous physical activity (MVPA) split [F (1,25) = 5.23, p = .03, η2 = 0.17], such that women who engaged in ≥45 min of average daily MVPA reduced their reaction time post-exercise (p = .01) and increased RT post-rest (p = .06). Time by session effects for spatial working memory 3-item accuracy and 4-item reaction time trended towards significance, p = 0.08 and p = 0.10, respectively, again driven by better performance post-exercise.
CONCLUSIONS: The moderate effect of acute exercise on domains of memory and processing speed in BCS is encouraging. Cancer-relatedcognitive impairment remains largely misunderstood; however, the results from the present study offer preliminary evidence for the positive relationship between acute exercise and cognition in BCS.
TRIAL REGISTRATION: ClinicalTrials.gov NCT02592070 . Registered 30 October 2015. Retroactively registered.

Coping with Post-chemotherapy Cognitive Impairment (PCCI)
Not many treatments for PCCI currently exist, although some patients may find relief from stimulants such as Ritalin®, commonly used to treat Attention Deficit Hyperactivity Disorder (ADHD). Ritalin can help improve mental focus, concentration and stamina in cancer patients.

People can use the following coping strategies to minimise the effects of PCCI:

- Exercise - even five minutes of mild to moderate activity may improve mental function
- Go for a walk
- Memory Aids - using a notebook, planner, cell phone, or list to keep track of things as they come to mind. A small recorder can also come in handy
- Also use your mobile phone, a calendar or daily planner to keep track of tasks, appointments, social commitments, birthdays etc
- Treat fatigue and sleep problems - these conditions can worsen PCCI symptoms
- Manage depression and anxiety - easing stress and elevating mood can ease PCCI symptoms
- Minimise distractions - a more soundproof environment, like an office or a cubicle in a different location can decrease distractions and improve concentration in the workplace
- Do mental exercises, such as crosswords
- Listen to music
- Plan the day to do the things that need the most thinking when feeling one's best and more alert, e.g. in the mornings
- Set aside time each day to read and respond to emails.
- Get extra rest
- Use a calendar and write down important dates and information
- Use a pill box to keep track of medications
- Try to keep one's life as simple as possible
- Avoid trying to do too many things at the same time
- Keeping one's mind active may help – for example, doing crosswords, sudoku and puzzles
- If you are working and have your own office, close the door when you don't want to be interrupted
- Put personal items (e.g. wallet, keys) in a dedicated place at home and at work so you don't misplace them
- Let phone calls go through to your answering machine or voicemail. You can listen to them and think about how you will respond when you feel ready
- Do tasks one at a time rather than multi-tasking
- Get plenty of sleep and exercise. Deep sleep is important for memory and concentration, and getting some physical activity every day will help you sleep better

Srivastava, R.K. & Singh, P. 2020.
"Chemo brain, a constellation of cognitive deficiencies followed by chemotherapy drugs, used to treat different types of cancers and adversely impacts the quality of life of a cancer survivor. The underlying mechanism of chemo brain remains vague, thus delaying the advancement of efficient treatments. Unfortunately, there is no US FDA approved medicine for chemo brain and often medicines considered for chemo brain are already the ones approved for other diseases. Nevertheless, researches exploring stem cell transplantation in different neurodegenerative diseases demonstrate that cellular transplantation could reverse chemotherapy-induced chemo brain. This review talks about the mechanism behind the cognitive impairments instigated by different chemotherapy drugs used in cancer treatment, and how stem cell therapy could be advantageous to overcome this disease."

Toh, Y.L., Sharig Muitaba, J., Bansal, S., Yeo, A., Shwe, M., Lau, A.J. & Chan, A. 2019.
STUDY OBJECTIVE: Dehydroepiandrosterone (DHEA) and its sulfated form (DHEAS)-jointly referred to as DHEA(S)-are neurosteroids known to regulate brain development and function that have been found to be positively correlated with cognitive function. It is unknown whether prechemotherapy plasma DHEA(S) levels are associated with the onset of cancer-related cognitive impairment (CRCI). The objective of this study was to evaluate whether an association exists between prechemotherapy plasma DHEA(S) levels and onset of CRCI in patients with breast cancer receiving chemotherapy.

DESIGN: Multicenter, prospective cohort study.
SETTING: Two specialized cancer centers in Singapore.
PATIENTS: Eighty-one patients with early-stage breast cancer (stages I-III) who had no prior exposure to chemotherapy and/or radiotherapy and were scheduled to receive anthracycline-based or taxane-based chemotherapy treatment with curative intent.
MEASUREMENTS AND MAIN RESULTS: Patients completed assessments for self-perceived and objective cognitive function at three time points: prechemotherapy (T1), during chemotherapy (T2), and after chemotherapy (T3). Plasma samples were collected prior to chemotherapy, and DHEA(S) levels were quantified by using ultra-high-performance liquid chromatography-tandem mass spectrometry. Multivariable logistic regression was used to adjust for clinically important factors and to evaluate the association between prechemotherapy plasma DHEA(S) levels and CRCI. Mean ± SD age was 48.9 ± 9.3 years, with 27.8% of patients experiencing clinically significant cognitive impairment based on global Functional Assessment of Cancer Therapy-Cognitive Function scores. The mean ± SD prechemotherapy plasma DHEAS and DHEA levels were 1.61 ± 0.91 μmol/L and 19.21 ± 13.13 nmol/L, respectively. Prechemotherapy DHEAS levels were found to be associated with impairment in the self-perceived cognitive domains of verbal fluency (adjusted odds ratio [OR] 0.27, 95% confidence interval [CI] 0.08-0.96) and mental acuity (adjusted OR 0.25, 95% CI 0.08-0.74). Conversely, DHEA levels were not associated with impairment in any cognitive subdomains.
CONCLUSION: Our findings suggest that patients with higher prechemotherapy DHEAS levels had lower odds of developing self-perceived cognitive impairment. Future studies are required to further investigate the effect of DHEA(S) on specific cognitive domains and to validate our findings in independent cohorts.

Lange, M., Joly, J., Ahles, T., Dubois, M., Tron, L., Winocur, G., De Ruiter, M.B. & Castel, H. 2019.
Background: Advances in diagnostic and therapeutic strategies in oncology have significantly increased the chance of survival of cancer patients, even those with metastatic disease. However, cancer-related cognitive impairment (CRCI) is frequently reported in patients treated for non-central nervous system cancers, particularly during and after chemotherapy.
Design: This review provides an update of the state of the art based on PubMed searches between 2012 and March 2019 on 'cognition', 'cancer', 'antineoplastic agents' or 'chemotherapy'. It includes the most recent clinical, imaging and pre-clinical data and reports management strategies of CRCI.
Results: Evidence obtained primarily from studies on breast cancer patients highlight memory, processing speed, attention and executive functions as the most cognitive domains impaired post-chemotherapy. Recent investigations established that other cancer treatments, such as hormone therapies and targeted therapies, can also induce cognitive deficits. Knowledge regarding predisposing factors, biological markers or brain functions associated with CRCI has improved. Factors such as age and genetic polymorphisms of apolipoprotein E, catechol-O-methyltransferase and BDNF may predispose individuals to a higher risk of cognitive impairment. Poor performance on neuropsychological tests were associated with volume reduction in grey matter, less connectivity and activation after chemotherapy. In animals, hippocampus-based memory and executive functions, mediated by the frontal lobes, were shown to be particularly susceptible to the effects of chemotherapy. It involves altered neurogenesis, mitochondrial dysfunction or brain cytokine response. An important next step is to identify strategies for managing cognitive difficulties, with primary studies to assess cognitive training and physical exercise regimens.
Conclusions: CRCI is not limited to chemotherapy. A multidisciplinary approach has improved our knowledge of the complex mechanisms involved. Nowadays, studies evaluating cognitive rehabilitation programmes are encouraged to help patients cope with cognitive difficulties and improve quality of life during and after cancer.

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