"Understanding 'Chemo Brain': From Biological Mechanisms to Survivorship Care"

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Abstract:
Deficits in memory, attention, executive function, and processing speed are hallmarks of Chemotherapy-Induced Cognitive Impairment (CICI), sometimes known as "chemo brain," a serious and frequently overlooked side effect of cancer treatment. This multidisciplinary review examines the intricate molecular processes underlying CICI, including neuroinflammation, oxidative stress, mitochondrial failure, and the direct neurotoxicity of chemotherapy drugs. Individual susceptibility to cognitive decline is influenced by both hereditary and epigenetic predispositions.
Clinically, CICI manifests as both objective and subjective symptoms that frequently affect a patient's mental health, everyday functioning, and quality of life. Due to symptom overlap with anxiety, sadness, and exhaustion, accurate diagnosis is still difficult and requires the use of cognitive tests, biomarkers, and neuroimaging. Treatment-related factors (drug kind, dosage, duration), patient characteristics (age, sex, genotype), and psychosocial conditions all affect how severe and long-lasting cognitive symptoms are.
Pharmacological methods, cognitive rehabilitation, lifestyle modifications, and psychosocial assistance are all part of the changing management regimens. Although they need further research, emerging treatments such as immunotherapy, regenerative medicine, and neuroprotective drugs show promise. Certain cancer populations, such as survivors of breast, lung, brain, and pediatric cancer, have different susceptibilities and outcomes, therefore customized strategies are required.
The significance of prevention, early intervention, and individualized survivorship care is also emphasized in this review. There is discussion of ethical and policy issues, emphasizing the necessity of improved patient communication and the incorporation of cognitive support into routine oncology treatment. To enhance therapeutic results and the general wellbeing of cancer survivors impacted by CICI, a patient-centered approach is necessary.

Keywords: Chemotherapy, Cognitive Impairment, Chemo brain, Neuroinflammation, Oxidative stress, Immunotherapy.

1. Introduction:

The cognitive impairments that many cancer patients and survivors endure during or after chemotherapy treatment are referred to as "chemo brain" or chemotherapy-induced cognitive impairment (CICI). These cognitive symptoms, which have a major impact on quality of life, frequently include executive dysfunction, memory loss, trouble focusing, and slowed processing speed.
Through an analysis of CICI's biological foundations, clinical presentations, risk factors, and management and survivorship care approaches, this review seeks to offer a thorough understanding of the condition.

2. Biological Mechanisms of Chemotherapy-Induced Cognitive Impairment (CICI)

CICI, sometimes known as "chemo brain," is a syndrome in which cancer survivors, especially after chemotherapy treatment, exhibit cognitive challenges such as memory loss, focus problems, and slower processing speeds. A number of significant biological processes, such as neuroinflammation, neurotoxicity, oxidative stress, and impairment of neurogenesis, are linked to CICI, even if the exact mechanisms are still

complicated and poorly understood. A thorough analysis of the biological processes behind CICI is provided below:

2.1 Neuroinflammation and Immune System Activation:

One of the primary mechanisms thought to contribute to this cognitive decline is neuroinflammation, which involves the activation of the brain's immune system, particularly microglia and astrocytes. Below is a review of the evidence that links chemotherapy with neuroinflammation and explores how this inflammation leads to cognitive dysfunction.

Neuroinflammation is a response to an inflammatory arrest in which the brain innate immune system is get activated. Moreover, there will be alterations in tissue homeostasis, protein aggregation abnormalities, trauma, ischaemia-associated damage, aging, toxins, and certain disease states. Neuroinflammation can be either acute or chronic (*Mechanisms Underlying Select Chemotherapeutic-Agent-Induced Neuroinflammation and Subsequent Neurodegeneration - Yahoo India Search Results*, n.d.). Peripheral inflammation also triggers for the neuroinflammatory actions through alteration of blood brain barrier (BBB) integrity. The BBB is made up of specialised endothelial cells joined tightly to prevent the entry of toxins into the peripheral nervous system. This tight junction allows the passage of only selective compounds across the BBB and prevents passive diffusion across it. Chemotherapy-mediated proinflammatory cytokines like tumour necrosis factor- alpha (TNF-α) and interleukin 1, 6 potentiates the permeability across the BBB, causing inflammatory responses in the brain (*Dysregulation of Cytokine Mediated Chemotherapy Induced Cognitive Impairment - Yahoo India Search Results*, n.d.). Now, this damage BBB allows the immune cells to enter and affect the CNS. Innate immune cells like monocytes, neutrophils, and adaptive immune cells like $CD4^+$ T cells $CD8^+$ T cells, and B cells are involved, which cause inflammatory mediators and vigorous the process of inflammation. Now, the innate immune response of the Central nervous system (CNS) activates the microglia and astrocytes. Microglia provide immunity to the CNS, and destroying the microorganism, removes debris, potentiates tissue repair to get back to tissue homeostasis (*Mechanisms Underlying Select Chemotherapeutic-Agent-Induced Neuroinflammation and Subsequent Neurodegeneration - Yahoo India Search Results*, n.d.).

2.2 Neurotoxicity of Chemotherapeutic Agents:

Chemotherapy-induced neurotoxicity encompasses a spectrum of central and peripheral nervous system (CNS and PNS) disorders that significantly impact patients' quality of life. These adverse effects can arise from both direct drug actions and indirect mechanisms such as inflammation, oxidative stress, and metabolic disturbances.

2.2.1Mechanisms of Chemotherapy-Induced Neurotoxicity

2.2.1.1 Neuroinflammation

Chemotherapeutic agents can activate glial cells—microglia and astrocytes—in the CNS, leading to the release of pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6. This neuroinflammatory response contributes to neuronal injury and dysfunction. For instance, cisplatin-induced neurotoxicity involves the activation of NF-κB, which alters hippocampal long-term potentiation. In contrast, bortezomib-induced peripheral neuropathy is associated with the upregulation of TNF-α and IL-6 in sensory neurons. Additionally, chemotherapy can disrupt the blood-brain barrier (BBB), allowing peripheral cytokines to enter the CNS and exacerbate inflammation (Gupta et al., 2022).

2.2.1.2 Oxidative Stress

Chemotherapeutic agents generate reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to oxidative stress that damages neuronal cells. For example, cisplatin-induced neurotoxicity involves dysregulation of the Nrf2/HO-1 pathway, impairing the cellular antioxidant defence system. This imbalance results in neuronal damage and cognitive deficits (Gupta et al., 2022)

2.2.1.3 Disruption of Neurotransmitter Systems

Chemotherapy can change neurotransmitter release and absorption, disrupting neural transmission. It has been demonstrated that medications such as cisplatin and carboplatin affect the release and uptake of dopamine and serotonin, which results in mood and cognitive deficits. Furthermore, by decreasing glutamate transporter expression, doxorubicin therapy damages glutamate neurotransmission, which leads to excitotoxicity and cognitive impairments.

2.2.1.4 Mitochondrial Dysfunction

Chemotherapeutic drugs can harm mitochondrial DNA and disrupt mitochondrial function, which increases the generation of reactive oxygen species and causes neuronal cell death. Oxaliplatin and cisplatin, for example, cause mitochondrial malfunction, which exacerbates peripheral neuropathy.

2.2.1.5 Autophagy Impairment

One cellular mechanism necessary for preserving neural homeostasis, autophagy, can be disrupted by chemotherapy. For instance, it has been demonstrated that doxorubicin inhibits neuronal autophagy, resulting in neuronal damage and cognitive impairments (Was et al., 2022).

2.2.2 Chemotherapy Agents Associated with Neurotoxicity

- **Platinum compounds**, such as oxaliplatin and cisplatin, are known to have neurotoxic effects, especially in the PNS, which can result in symptoms such peripheral neuropathy.
- **Methotrexate (MTX):** Cognitive deficits are a result of MTX-induced neurotoxicity, which includes neuroinflammation, oxidative stress, and disruption of neurotransmitter systems.
- **Doxorubicin (DOX):** Neuronal damage and cognitive dysfunction result from DOX's impairment of autophagy and glutamate neurotransmission (Was et al., 2022).
- **Bortezomib:** This proteasome inhibitor uses oxidative stress and inflammation to cause peripheral neuropathy (Zajączkowska et al., 2019).

Management and Neuroprotective Strategies

There aren't any well recognized therapies to stop chemotherapy-induced neurotoxicity at the moment. Nonetheless, the following tactics are being studied:

- **Anti-inflammatory Agents:** In preclinical models, medications such as thalidomide and IL-10 have demonstrated potential in lowering neuroinflammation and easing the symptoms of neuropathy (Vichaya et al., 2015)
- **Antioxidants:** Enhancers of the Nrf2/HO-1 pathway may reduce oxidative stress and guard against damage to neurons (Gupta et al., 2022)**.**
- **Autophagy Modulators:** Restoring autophagic function may help preserve neuronal homeostasis and avoid cognitive impairments brought on by chemotherapy.

2.2.3 The impact of chemotherapy on neurogenesis and neuroplasticity, especially in regions like the hippocampus.

The hippocampus, a key area for memory, learning, and emotional control, is particularly vulnerable to the profound effects of chemotherapy on neurogenesis, or the production of new neurons, and neuroplasticity, or the brain's capacity for structural and functional adaptation.

2.2.3.1. Impaired Neurogenesis in the Hippocampus

Adult neurogenesis involves neural stem cells (NSCs) and progenitor cells moving through distinct stages before integrating as mature neurons in the subgranular zone of the hippocampus dentate gyru (Was et al., 2022)**.** In both animal models and cell cultures, it has been demonstrated that chemotherapeutic agents such as cisplatin, cyclophosphamide (CP), methotrexate (MTX), 5 fluorouracil (5 FU), carmustine, AraC, and doxorubicin (DOX) decrease proliferation markers (Ki 67, BrdU) and immature neurons (DCX) (Fernandez et al., 2020)**.** Even years after therapy, human hippocampus tissue from cancer survivors shows a 10-100 fold decrease in immature DCX^+ neurons (Lomeli et al., 2021).

2.2.3.2. Suppression of Adult Hippocampal Neurogenesis

In the dentate gyrus subgranular zone (SGZ) and subventricular zone (SVZ), the proliferation of neural stem/progenitor cells is inhibited by chemotherapeutic drugs such as methotrexate (MTX), 5 fluorouracil (5 FU), cisplatin, carmustine, cytarabine, cyclophosphamide (CP), and doxorubicin (DOX). After these therapies, there is a considerable drop in proliferation markers like Ki 67 and immature neurons like doublecortin (DCX) (Fernandez et al., 2020). In preclinical rodent studies, temozolomide (TMZ) reduced new cell numbers in the granule cell layer by ~34 50%, impairing learning tasks dependent on hippocampal neurogenesis. Chemotherapy alters the adult brain's theta activity, neurogenesis, and learning. These decreases frequently last for weeks following the end of treatment. (Fernandez et al., 2020)

2.2.3.3. Impairments in Neuroplasticity & Neuronal Structure

Chemotherapy disrupts the integrity of dendritic architecture, including decreases in dendritic branching and spine density in hippocampal CA1, CA3, and dentate gyrus neurons, undermining synaptic connectivity (Bradley-Garcia et al., 2022)**.** Functional plasticity is also reduced: several agents (e.g., DOX,

cisplatin) impair long-term potentiation (LTP), a critical mechanism underlying learning and memory (Was et al., 2022). Theta-rhythm oscillations (4–10 Hz) in the hippocampus—important for temporal associative learning—are attenuated after chemotherapy, correlating with impaired learning performance (Nokia et al., 2012).

2.2.3.4. Inflammation, Oxidative Stress & Molecular Mediators

Systemic chemotherapy induces neuroinflammation, with increased levels of pro-inflammatory cytokines such as IL-6, TNF-α, and decreased anti-inflammatory cytokines like IL-10, in both serum and hippocampal tissue (Shi et al., 2019). This inflammatory cascade contributes to blood–brain barrier disruption, microglial activation, and hippocampal damage. Elevated oxidative stress markers (e.g. 8-OHdG) and activation of stress pathways (ERK/JNK kinases) are observed in the hippocampus following chemotherapy, linking to DNA/RNA damage and neural cell (Bagnall-Moreau et al., 2019).

2.2.3.5. Cognitive and Functional Consequences

Rodent models show chemotherapy-treated animals performing poorly on hippocampus-dependent cognitive tasks such as spatial water maze, delayed non-matching to sample, and associative conditioning (Winocur et al., 2014). In human studies, cognitive domains particularly affected include episodic memory, attention, executive function, and processing speed—consistent with structural and functional disruption of the hippocampus and connected networks (Pereira Dias et al., 2014). Neuroimaging of cancer survivors reveals reduced hippocampal volume and connectivity, with correlations to cognitive symptoms (Bradley-Garcia et al., 2022).

2.2.3.6. Potential Protective Interventions

Aerobic exercise prevents chemotherapy-induced suppression of hippocampal neurogenesis in rodents and preserves cognitive performance (Winocur et al., 2014). Environmental enrichment, cognitive stimulation, and pharmacological agents (e.g., anti-inflammatories, antidepressants) have shown promise in restoring neurogenesis and improving mood/cognition post-chemotherapy (Pereira Dias et al., 2014). Interventions targeting inflammation (e.g. cytokine modulators), oxidative damage pathways (e.g. antioxidants), or neurotrophic enhancement have been proposed as neuroprotective strategies (Bagnall-Moreau et al., 2019).

Summary Table 1

Chemotherapy—especially regimens involving antimitotic agents—selectively suppresses adult hippocampal neurogenesis and disrupts synaptic structure and functional plasticity. These effects, often mediated via inflammation, oxidative stress, and structural damage in hippocampal subfields, underlie the cognitive impairments reported in both animal models and human survivors of cancer. Interventions that promote activity-dependent neurogenesis (e.g., physical exercise) or reduce inflammation/oxidative injury may help mitigate these consequences.

2.3 Oxidative Stress and Mitochondrial Dysfunction:

Chemotherapy triggers oxidative stress in the brain. Many chemotherapeutic agents—including cisplatin, doxorubicin, cyclophosphamide, methotrexate, and mitoxantrone—generate reactive oxygen species (ROS) and reactive nitrogen species (RNS), driving oxidative and nitrosative stress both systemically and within the CNS (Was et al., 2022). Some agents like doxorubicin do not cross the blood-brain barrier (BBB) directly, but induce peripheral release of→ TNF-α, which crosses into the brain and enhances oxidative damage and inflammation (Rummel et al., 2021).

1. Neuronal damage via oxidative DNA/RNA damage, neuroinflammation & apoptosis.

Elevated ROS in neurons leads to oxidative damage to DNA and RNA, such as increased 8-OH(d)G and 8-OHG lesions in hippocampal rRNA and DNA, impairing protein synthesis and genomic integrity (Bagnall-Moreau et al., 2019).

Neuroinflammation is concurrently activated: chemokine and cytokine pathways (IL-6, TNF-α, NF-κB, MAPKs including JNK/ERK/p38) are upregulated and cause neuronal dysfunction, apoptosis, and demyelination (Bagnall-Moreau et al., 2019).

This drives neuronal loss, decreased dendritic spine density, synaptic plasticity deficits, and impaired neurogenesis (e.g. lower BDNF, fewer newborn neurons) in cognition-relevant brain regions like the hippocampus and prefrontal cortex (Murillo et al., 2023), (Rummel et al., 2021), (Ibrahim et al., 2024).

2. Mitochondrial dysfunction and impaired energy metabolism.

ROS damages mitochondria directly: cisplatin binds mitochondrial DNA (mtDNA), forming adducts and disrupting transcription/translation of ETC components; this leads to reduced respiratory capacity (complex

I, II, IV), ATP depletion, and elevated ROS—a vicious cycle (Murillo et al., 2023). Doxorubicin-treated rodents show decreased mitochondrial respiratory chain activity, high H_2O_2 emission, increased permeability transition pore (mPTP) opening, and reduced ATP production in hippocampal mitochondria (Murillo et al., 2023).

Mitoxantrone similarly reduces ATP synthase expression, lowers antioxidant enzyme (MnSOD) levels, increases oxidative markers, and alters autophagy and synaptic proteins like PSD-95 in hippocampus and prefrontal cortex (Dias-Carvalho et al., 2022). Chemotherapy also impairs endogenous antioxidant systems: depletion of GSH, reduced superoxide dismutase (SOD) and catalase activity, downregulation of Nrf2 pathway—all amplify oxidative damage (Rummel et al., 2021).

3. Linking neuronal & mitochondrial damage to cognitive decline.

Structural changes—loss of dendritic spines, reduced neurogenesis, synaptic density loss—and biochemical deficits in hippocampus and frontal cortex translate into measurable cognitive impairment in animal models: impaired performance on memory tasks such as novel object recognition, spatial learning, and social discrimination after treatment with cisplatin, doxorubicin, or AC-chemotherapy (doxorubicin + cyclophosphamide) (Murillo et al., 2023). This phenomenon is collectively termed "chemobrain" or chemotherapy-related cognitive impairment (CRCI) and is thought to accelerate brain aging and impair executive function, working memory, and episodic memory (Dias-Carvalho et al., 2022).

Protective strategies (experimental evidence)

- **Exercise** (e.g. low-intensity treadmill) in rodent models mitigates hippocampal mitochondrial dysfunction, reduces ROS, preserves BDNF, and improves cognition after doxorubicin treatment (Rummel et al., 2021).
- **Antioxidants** such as N-acetylcysteine, astaxanthin, acetyl-L-carnitine, berberine, resveratrol, and gamma-glutamylcysteine ethyl ester (GCEE) showed neuroprotective effects by restoring GSH, boosting Nrf2/SIRT1 pathways, and reducing oxidative/inflammatory markers (Bagnall-Moreau et al., 2019), (Rummel et al., 2021), (Was et al., 2022), (Ibrahim et al., 2024).

2.4 Genetic and Epigenetic Factors in CICI:

Genetic predisposition to CICI—with a focus on polymorphisms in key genes involved in inflammation, oxidative stress, and neuronal survival:

2.4.1. APOE (Apolipoprotein E)

The APOE ε4 allele—a well-known risk factor for Alzheimer's disease—is also linked to higher risk of CICI following chemotherapy. APOE-ε4 carriers show greater oxidative stress, neuroinflammation, and blood–brain barrier disruption, all of which overlap with chemotherapy pathophysiology (Fernandez et al., 2020). Studies of breast and lymphoma survivors treated with chemotherapy showed that ε4 carriers performed worse on visual memory, spatial ability, and psychomotor tasks compared to non-ε4 carriers (Cheng et al., 2016). However, a large longitudinal prospective CANTO-Cog study (2025) with early-stage breast cancer patients found no overall association between APOE-ε4 status and CRCI over 4 years, nor strong interaction with chemotherapy; some domain-specific differences in attention and memory emerged only among certain groups (e.g., endocrine-therapy treated) (Duivon et al., 2025).

2.4.2. BDNF (Brain-Derived Neurotrophic Factor)

The functional polymorphism Val66Met (rs6265) affects neuroplasticity and memory. In non-cancer populations, the Met allele is associated with poorer memory/executive functioning and lower hippocampal volume. There is limited evidence directly linking BDNF polymorphisms to CRCI currently, but based on its established role in neuronal repair and plasticity, BDNF is considered a plausible genetic modifier of post-chemotherapy cognitive outcomes (Ahles & Saykin, 2007)

2.4.3. COMT (Catechol-O-Methyltransferase)

The COMT Val158Met polymorphism (rs4680) and linked variants (e.g. rs165599) modulate dopamine metabolism in the prefrontal cortex. In breast cancer survivors receiving chemotherapy, carriers of the Val allele (Val/Val or Val/Met) show greater susceptibility to deficits in executive function and working memory compared to Met/Met individuals (Cheng et al., 2016).

2.4.4. Glutathione-S-Transferases (GSTs): GSTM1, GSTT1, GSTP1

GSTM1 null genotype (gene deletion) removes expression of a key phase II detox enzyme and reduces antioxidant defense capacity. In pediatric medulloblastoma survivors, the combined GSTM1-null and GSTT1-null genotype predicted more severe intellectual impairment and learning deficits after treatment, implicating

oxidative-stress mediated neurotoxicity (Barahmani et al., 2009). Though many studies focus on cancer risk or survival, little direct evidence links GSTM1 to adult CRCI—but the same oxidative mechanisms suggest it is a plausible modifier. GSTP1 Ile105Val polymorphism also influences detoxification efficiency: For example, in colorectal cancer patients receiving oxaliplatin, the GSTP1 105Ile homozygous genotype was associated with more severe cumulative neuropathy, likely reflecting impaired detoxification and oxidative damage in neurons (Lecomte et al., 2006). While neuropathy is peripheral rather than cognitive, the oxidative-stress sensitivity suggests potential relevance to CNS effects.

2.4.5. Other antioxidant enzyme polymorphisms

Polymorphisms in GPX1 (e.g. Pro198Leu, rs1050450) and catalase (CAT) (e.g. rs7943316) affect antioxidant enzyme activity. In leukemia risk studies, variants in GPX1 and CAT were associated with altered oxidative stress handling and disease risk (Kagita et al., 2021). Their impact on cognitive outcomes after chemotherapy has not been directly studied, but it remains mechanistically plausible. Summary Table 2

3. CLINICAL PRESENTATION AND DIAGNOSIS OF CICI

Chemotherapy has been consistently associated with cognitive impairments across several domains—a phenomenon often referred to as chemotherapy-induced cognitive impairment (CICI) or "chemobrain". Below is a breakdown of the cognitive domains most commonly affected by chemotherapy, along with supporting research evidence:

3.1 Cognitive Domains Affected by Chemotherapy:

3.1.1. Attention and Concentration

- **Description**: Difficulty focusing, sustaining attention, or switching between tasks.
- **Clinical Evidence**: Breast cancer survivors often report challenges in maintaining attention during conversations or multitasking.
- **Neuropsychological tests used**: Continuous Performance Test (CPT), Digit Span, Trail Making Test A.
- **Mechanisms**: Associated with **prefrontal cortex dysfunction**, inflammation, and dopamine pathway alterations (e.g., COMT polymorphism) (Janelsins et al., 2014)**.**

3.1.2 Executive Function

- **Description**: Problems with planning, organizing, problem-solving, and flexible thinking.
- **Clinical Evidence**: Reported in patients after high-dose chemotherapy or brain irradiation.
- **Tests used**: Wisconsin Card Sorting Test (WCST), Stroop Test, Trail Making Test B.
- **Mechanisms**: Linked to **frontal lobe dysfunction**, reduced dopamine activity, and neuroinflammatory pathways (Ahles & Saykin, 2007)**.**

3.1.3. Working Memory

- **Description**: Difficulty holding and manipulating information over short periods.
- **Tests used**: N-back test, Digit Span Backwards.
- **Clinical Relevance**: Affects academic/work performance and real-life tasks (e.g., remembering a phone number).
- **Mechanisms**: Changes in **hippocampal-prefrontal circuitry**, mitochondrial dysfunction, and neurotransmitter imbalance (McDonald, 2013)**.**

3.1.4. Processing Speed

- **Description**: Slowed mental processing; taking longer to complete tasks or respond.
- **Tests used**: Symbol Digit Modalities Test, Coding subtest of WAIS, Trail Making Test A.
- **Clinical Impact**: Often noticed in everyday tasks requiring fast thinking or decision-making.
- **Mechanisms**: White matter damage, disrupted connectivity, oxidative stress (Wefel et al., 2011)**.**

3.1.5. Learning and Memory (Verbal and Visual)

- **Description**:
  - **Verbal memory**: Difficulty recalling conversations or written material.
  - **Visual memory**: Problems remembering images or spatial locations.
- **Tests used**: Rey Auditory Verbal Learning Test (RAVLT), Hopkins Verbal Learning Test, Visual Reproduction (WMS).
- **Mechanisms**: Damage to **hippocampus**, reduced neurogenesis, BDNF suppression (Kesler et al., 2013)

3.1.6. Language (Verbal Fluency and Naming)

- Description: Word-finding difficulty, slower verbal output, reduced fluency.

- Tests used: Category and Letter Fluency tasks (e.g., FAS test).
- Clinical Impact: Patients report "tip-of-the-tongue" problems or difficulty expressing thoughts clearly (Ahles et al., 2002).

3.1.7. Visuospatial Function

- Description: Difficulty with spatial orientation or visual-motor tasks.
- Tests used: Block Design, Rey-Osterrieth Complex Figure Test (copy task).
- Mechanisms: Altered parietal cortex activity or connectivity; more common in older patients.

[30].

3.1.8. Memory

Verbal memory (e.g., word list learning, story recall) is one of the domains most frequently shown to decline post-chemotherapy. Meta-analytic evidence demonstrates small to moderate effect sizes for verbal memory deficits in those receiving chemotherapy compared to controls or pre-treatment baseline [30].

Visuospatial memory is also notably affected, with some studies reporting larger impairments in this domain than verbal memory (Hwang et al., 2021), (Oliva et al., 2024), (Yang & Von Ah, 2024). Long-term studies (e.g., >20 years post-treatment) confirm persistent deficits in verbal learning and memory among survivors treated with chemotherapy (Hardy et al., 2018).

Attention & Working Memory

- Impairments in sustained attention and concentration are often reported, particularly during and immediately after chemotherapy treatment (Oliva et al., 2024)
- Working memory—which includes information updating and manipulation—is frequently compromised.

Rodent-model meta-analysis also supports working-memory deficits as a common outcome of chemotherapy exposure (Oliva et al., 2024).

Processing Speed

- Reduced processing speed (e.g., slower reaction times, slower symbol-digit or coding tasks) is regularly observed—often among the most consistently impaired domains across studies (Rodríguez Martín et al., 2020).
- Prospective studies show decline in processing speed during chemotherapy that may persist over time, sometimes with incomplete recovery at 1 year or beyond (Hardy et al., 2018)

3.2 Assessment Tools for CICI and role of biomarkers in diagnosing CICI.

3.2.1 Mini-Mental State Examination (MMSE)

- Overview: A 30-point, approximately 5-10 min clinician-administered questionnaire testing orientation, registration, attention/calculation, recall, language, and simple visuospatial copying (Magnuson et al., 2016).
- Strengths: Quick, widely used, minimal training required.
- Limitations: Low sensitivity for mild cognitive impairment and executive/visuospatial deficits—less suitable for detecting subtle changes seen in cancer survivors.

3.2.2 Montreal Cognitive Assessment (MoCA)

- Overview: Also a 30-point test (~10 min), covering attention, executive/visuospatial function (e.g. clock drawing, cube copy), memory, language, abstraction, and orientation (Matsui et al., 2022).
- Strengths: Higher sensitivity for mild impairment (~90% sensitivity vs. ~18% for MMSE in other populations); better coverage of executive and visuospatial domains.
- Evidence in oncology: Among older adults with cancer, 66.7% screened positive with MoCA versus only 19.7% with MMSE ($p < 0.0001$) (Rambeau et al., 2019). In brain metastasis patients, MoCA identified impairment in 80% of cases versus 30% with MMSE (Olson et al., 2008).
- Feasibility: Completed within 10 min in ~88% of cancer patients, with good tolerability (Olson et al., 2008).

3.2.3 Mini-Cog, Clock Drawing Test (CDT), BOMC, SPMSQ

- Mini-Cog: Two-item memory recall plus clock-drawing; ~3 min; good utility in diverse, low-literacy older cancer populations (sensitivity ~80%, specificity ~84%) (Magnuson et al., 2016).
- Clock Drawing Test (CDT): Quick visuospatial/executive screen, often used with MoCA/MMSE for CRCI screening (Isenberg-Grzeda et al., 2017).
- BOMC (Blessed Orientation–Memory–Concentration): Six-item test with sensitivity for mild to severe deficits, less influenced by education level (Magnuson et al., 2016).

- SPMSQ (Short Portable Mental Status Questionnaire): 10-item orientation and memory screen, easy to administer in clinical settings.

3.2.4 The role of biomarkers (e.g., BDNF, cytokines) and neuroimaging (e.g., MRI, PET scans) in diagnosing CICI

3.2.4.1 Brain-Derived Neurotrophic Factor (BDNF)

A systematic review found that plasma or serum BDNF levels were positively associated with better cognitive outcomes in about 56% of studies involving cancer patients and survivors. Neuroimaging studies also observed structural and functional links in 3 of 7 cases reviewed (Yap et al., 2021), (D. Q. Ng et al., 2022).

A longitudinal pilot in breast cancer patients showed that declines in BDNF post-chemotherapy were significantly associated with self-perceived concentration deficits, even after adjusting for confounders like age or genotype (T. Ng et al., 2017).

In early-stage breast cancer, higher plasma levels of pro-inflammatory cytokines—such as IL-6, IL-1β, IL-4, IL-8, IFN-γ, TNF-α—were inversely correlated with BDNF levels, especially among those with persistent CRCI. The IL-6 × persistent-impairment interaction reached statistical significance ($p = 0.026$) (Yap et al., 2021).

3.2.4.2 Cytokines & Inflammation

Reviews show that elevated **IL-6**, **IL-1β**, **TNF-α**, and soluble TNF receptor II (sTNFRII) correlate with poorer cognitive performances, particularly executive function and processing speed (Castel et al., 2017). In chemotherapy-treated breast cancer survivors, clusters of cytokines (IL-1β, IL-2, IL-4, IL-7, IL-8, TNF-α, IFN-γ, MCP-1) alongside demographic variables explained up to **71%** of variance in objective cognitive scores (Schroyen et al., 2022). Some studies report IL-4 might be neuroprotective, with higher levels associated with better speed and fewer self-reported cognitive complaints (Castel et al., 2017). BDNF shows promise as a marker of neuroplasticity and cognitive resilience, while pro-inflammatory cytokines—especially IL-6, IL-1β, TNF-α—are consistently elevated in cases of CRCI and correlate with poorer performance.

3.2.4.3 Neuroimaging Markers: MRI, DTI & PET

Structural MRI & Voxel-Based Morphometry (VBM)

A meta-analysis of MRI studies in cancer survivors found gray matter reductions in frontal and temporal regions post-chemotherapy, often correlating with cognitive deficits (Niu et al., 2021). Individual case studies (e.g., monozygotic twins discordant for chemo exposure) show that the treated twin displayed widespread activation increases during working memory tasks—suggesting compensatory neural recruitment despite preserved test scores

Diffusion Tensor Imaging (DTI)

Review of DTI studies reveals compromised white matter integrity—such as reduced fractional anisotropy—in patients after non-CNS chemotherapy. Importantly, these structural changes correlate with declines in cognitive domains like attention, processing speed, and executive function (Deprez et al., 2013).

Functional Imaging & PET

Functional MRI and FDG–PET studies reveal ** hypo- or hyper-activations** in frontal cortex, cerebellum, and inferior frontal gyrus—areas implicated in attention, working memory, and short-term memory tasks—all showing altered metabolic activity post-chemotherapy.

3.3 Impact of CICI on Daily Life:

CICI, or "chemobrain" impacts Quality of life (QoL), work functioning, and personal relationships, supported by both qualitative and quantitative research:

3.3.1 Quality of Life (QoL)

Even mild cognitive changes—like memory lapses or mental fog—have been shown to significantly reduce cancer survivors' quality of life, self-confidence, and self-image. Many feel they have lost part of who they were, describing symptoms like memory loss or difficulty multitasking as undermining their identity. Disruptions in information processing (DIPs)—a term describing slowed or fragmented thinking—are linked to lower role satisfaction, reduced engagement in social roles, elevated anxiety and frustration, and poor overall well-being among breast cancer survivors (Bailey et al., 2024).

A Chinese cross-sectional study found that ~79% of breast cancer survivors reported mild cognitive impairment, and these deficits correlated with lower self-care ability and reduced QoL. Self-care ability partially mediated (~22–24%) the cognitive impairment–QoL relationship (Wu et al., 2024).

3.3.2 Functioning at Work

Qualitative reports reveal that survivors frequently experience reduced concentration, increased distractibility, and mental exhaustion ("ADD-like" symptoms), making previously routine tasks mentally draining. Women recount slower productivity, missed details, inability to multitask, and diminished confidence—leading to missed promotions, changes in roles, or even job loss. Some felt forced to shift to less demanding roles, earning significantly less (~$25–30K less annually).

One participant described being "totally useless" for years post-treatment in a once highly demanding engineering-manager role. Eventually, she declined to less technical and lower-paid work due to persistent cognitive difficulties.

Delayed processing, difficulty following meetings, or sustaining focus can impair professional identity and decision-making about returning to work and affect re-entry into schooling or competitive academic environments.

Reddit users also describe work struggles: one software developer reported inability to focus, slowed throughput, and lack of concentration affecting code quality—mirroring real-world performance declines (Boykoff et al., 2009).

3.3.3 Impact on Personal Relationships

Cognitive deficits can strain relationships: family members may respond with lack of understanding, dismissiveness, or frustration—compounding feelings of helplessness and isolation (Boykoff et al., 2009). Survivors often report altered personal identity: feeling less capable or less lovable, with a diminished sense of agency—leading to self-blame or a perception that they've let loved ones down. Many hide cognitive struggles, especially from strangers or acquaintances, due to shame or fear of judgment. This secrecy can add emotional burden and contribute to social withdrawal or isolation. Increased emotional sensitivity means some survivors find it difficult to respond to stress or distractions from others—triggering emotional or relational friction with partners, especially on "bad" cognitive days (Henderson et al., 2019).

4. DISCUSSION

CICI, commonly referred to as "chemo brain," represents a significant and multifactorial side effect of cancer treatment, impacting a substantial proportion of cancer survivors. The biological underpinnings of CICI are complex and involves an interplay of neuroinflammation, direct neurotoxic effects of chemotherapeutic agents, oxidative stress, and genetic susceptibility. Evidence consistently highlights the roles of cytokine dysregulation (e.g., IL-6, TNF-α), microglial activation, blood-brain barrier disruption, and impaired neurogenesis—particularly in hippocampal regions—as key mechanisms driving cognitive decline (Ahles & Root, 2018).

The clinical manifestation of CICI spans several cognitive domains, including memory, executive functioning, processing speed, and attention. Patients frequently report subjective symptoms such as mental fog, forgetfulness, and decreased concentration, which are often underestimated in clinical settings (Janelsins et al., 2014). Neuropsychological tools, neuroimaging, and biomarkers such as BDNF and pro-inflammatory cytokines are useful in assessing and monitoring cognitive changes, although their clinical implementation remains limited by variability and accessibility.

Risk factors for CICI are both treatment-related (e.g., dose, type, and duration of chemotherapy) and patient-related (e.g., age, sex, genetic polymorphisms such as *APOE ε4* and *GSTM1* deletions). Pre-existing psychological conditions (e.g., depression, anxiety), socioeconomic status, and cognitive reserve further modulate vulnerability. Pediatric populations and older adults may be particularly at risk due to developmental and age-related vulnerabilities, respectively.

Management of CICI remains a major clinical challenge. While pharmacological agents such as modafinil, SSRIs, and donepezil have shown limited and variable benefits, non-pharmacological strategies such as cognitive rehabilitation, mindfulness, exercise, and psychosocial interventions offer more promising outcomes. These lifestyle and behavioral approaches not only target cognitive recovery but also improve overall psychological resilience (Lange et al., 2019).

Despite increasing awareness, CICI remains underdiagnosed and under-addressed in routine oncology care. Survivors often face long-term implications for their quality of life, employment, and psychosocial well-being, with many reporting persistent symptoms years after treatment completion. Additionally, emerging cancer therapies such as immunotherapy introduce new concerns for neurotoxicity and cognitive function, further complicating survivorship care.

5. CONCLUSION

Chemotherapy-induced cognitive impairment is a significant, multifaceted consequence of cancer therapy that extends well beyond the acute treatment phase. The interplay of neuroinflammatory responses, oxidative stress, direct neurotoxic effects, and individual genetic predispositions underscores the biological complexity of CICI. Clinically, its manifestations can be profound, affecting day-to-day functioning and diminishing survivors' quality of life.

Current assessment and management strategies remain inadequate to fully address the scope of this issue. There is a pressing need for standardized diagnostic tools, early identification protocols, and effective, personalized interventions. A paradigm shift is required in survivorship care to incorporate cognitive health as a critical component of post-treatment monitoring and rehabilitation. Furthermore, patient-centered care, including the use of patient-reported outcomes, must become a routine part of oncology practice to better capture the lived experience of cognitive dysfunction.

6. Future Perspectives

Future research should focus on several critical areas to improve outcomes for patients experiencing CICI:

1. **Biomarker Discovery and Validation**: Continued efforts are needed to identify reliable peripheral and central biomarkers (e.g., inflammatory cytokines, neurofilament light chain, BDNF) for early detection, monitoring, and treatment response evaluation.
2. **Neuroimaging and Digital Tools**: Advanced imaging techniques and digital cognitive tracking tools, including machine learning-based assessments, can offer more sensitive and longitudinal insights into CICI progression.
3. **Personalized Medicine Approaches**: Incorporating pharmacogenomics and genetic profiling (e.g., *APOE*, *COMT*, *GSTM1*) could allow for individualized chemotherapy regimens with lower neurotoxicity risk.
4. **Neuroprotective and Regenerative Therapies**: Research into neuroprotective agents (e.g., omega-3 fatty acids, antioxidants), neurotrophic factors, and even regenerative strategies such as stem cell therapy holds promise for mitigating or reversing CICI.
5. **Integration into Survivorship Programs**: National healthcare policies should mandate the inclusion of cognitive assessment and rehabilitation in survivorship care plans. Reimbursement and training for cognitive rehabilitation services should be expanded.
6. **Longitudinal and Pediatric Research**: Long-term studies are needed to understand how CICI evolves across decades, especially in pediatric cancer survivors whose neurodevelopment may be disrupted during critical growth periods.
7. **Impact of Emerging Therapies**: As novel cancer treatments like immunotherapies and CAR-T cell therapies become more common, it is essential to investigate their potential cognitive side effects and mechanisms distinct from traditional chemotherapeutics.
8. **Educational and Communication Strategies**: Oncology care teams must improve communication around the risks of CICI, integrating shared decision-making tools and educational resources to prepare patients and families for potential cognitive side effects.

As the population of cancer survivors grows, addressing CICI must become a priority not only to extend life but to preserve its quality.

Declarations

Author contribution

UL: Wrote the manuscript, prepared the tables. Carefully reviewed and submitted the manuscript.

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Abbreviation:

CICI: Chemotherapy-induced cognitive impairment
BBB: Blood brain barrier
TNF-α: Tumour necrosis factor- alpha
CNS: Central nervous system
ROS: Reactive oxygen species
RNS: reactive nitrogen species
MTX: Methotrexate
DOX: Doxorubicin
SGZ: Subgranular zone
SVZ: Subventricular zone
mtDNA: Mitochondrial DNA
SOD: Superoxide dismutase
CRCI: Chemotherapy-related cognitive impairment
COMT: Catechol-O-Methyltransferase
GSTs: Glutathione-S-Transferases
CAT: Catalase
RAVLT: Rey Auditory Verbal Learning Test
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
CDT: Clock Drawing Test
BDNF: Brain-Derived Neurotrophic Factor
VBM:. Voxel-Based Morphometry
DTI: Diffusion Tensor Imaging
QoL: Quality of Life
DIPs: Disruptions in information processing

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