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Chemotherapy-Induced Cognitive Decline: Moving from the Mechanistic Debate towards Prevention and Treatment—A Clinical Review

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Abstract

Patients receiving chemotherapy have reported cognitive challenges including short-term memory loss and reduced executive functioning. While cognitive decline can be multifactorial and related to aging, depression, surgery, and other medications, there has been a steadily increasing body of knowledge showing a significant association between cognitive decline and chemotherapy administration. This clinical review summarizes patient-reported cognitive changes, support from neuroimaging and neuropsychological testing. The mechanism of action of and patient susceptibilities to cognitive decline are reviewed. Current behavioral and pharmacologic interventions are discussed. There is a need to identify patients at risk for developing chemotherapy induced cognitive decline and to screen for early signs of cognitive deterioration. The risk of cognitive dysfunction and possible interventions should be included in the informed consent discussion with patients who are undergoing cytotoxic treatments.

Keywords

Chemotherapy, Cognitive Decline, Cognitive Impairment, Chemo-Brain, Chemo-Fog, Cancer Survivorship, Quality of Life

1. Introduction

Recent advances in the diagnosis and treatment of cancer have led to an increased number of patients entering survivorship [1] [2]. Increased survival rates dictate that more resources should be directed towards diagnosing and managing the issues affecting patients' post-treatment quality of life. Among these,

chemotherapy-induced cognitive decline (CICD) has emerged as an important sequelae of therapy.

The paramount challenge in any discussion of CICD is discerning the potential cognitive harms of cytotoxic drugs from an assortment of possible confounders, including age-related cognitive deterioration, the adverse effects of concurrent treatment modalities, and disease-related factors stemming from the cancer itself (**Table 1**) [3]-[19]. For instance, long-term adjuvant endocrine therapy (ET) is a standard treatment for hormone-positive breast cancer (BC) and is a plausible etiology for cognitive dysfunction in treated women [4] [5] [6]. While some studies have reported ET-related cognitive impairments over a short-term follow-up period, a recent longitudinal study which observed ET-treated patients for up to six years failed to demonstrate such an association [7]. Major oncological surgery is another candidate mechanism, with data showing post-surgical cognitive decline in a substantial percentage of patients, most notably in elderly populations [8]. Chronic opioid usage for management of cancer-related pain is similarly associated with cognitive deficits in a dose-related manner [9].

Table 1. Evidence for possible culprits responsible for cognitive decline in cancer patients, other than chemotherapy.

Cluster	Etiology	Reference	Study Design	Findings
Iatrogenic	Long-term adjuvant endocrine therapy	*Van Dyke, et al.* [7]	Prospective longitudinal	No association found between long-term endocrine therapy and neurocognitive performance
	Major oncologic surgery	*Plas M, et al.* [8]	Prospective longitudinal	- 12% of patients overall exhibit cognitive decline at 3-months following major oncologic surgery - 18% of patients aged >75 years exhibit cognitive decline at 3 months following major oncologic surgery
	Chronic opioid usage	*Kurita GP, et al.* [9]	Prospective cross-sectional, multi-center	- A third of opioid-treated patients exhibit possible (MMSE[a] score 24 - 26) or definite (MMSE score < 24) cognitive dysfunction - Patients receiving daily dose of 400 mg or more had 1.75 times higher odds of having a lower MMSE score compared with those receiving daily dose lower than 80 mg
Cancer-related comorbidities	Post-traumatic stress	*Hermelink, et al.* [18]	Prospective longitudinal	Cancer patients exhibited subtle cognitive deficits, irrespective of chemotherapy, which is mediated by post-traumatic stress
	Fatigue	*Menning, et al.* [13]	Prospective longitudinal	Cancer patients exhibited cognitive impairment prior to receipt of chemotherapy; effect was mediated by fatigue and not observed when fatigue accounted for
	Depression	*Polsky, et al.* [14]	Prospective longitudinal	Hazard Ratio = 3.55 (95% CI 2.79 - 4.52) for depressive symptoms within 2 years following a cancer diagnosis
Other	Age-related cognitive decline	*American Cancer Society* [3]	Epidemiologic	47% of cancer survivorships in the US is 70 years of age or older

[a]Mini Mental State Examination.

In terms of disease-related factors, pretreatment cognitive impairment is a well-established entity not only in chemo-naïve patients but also prior to any intervention whatsoever [10] [11] [12]. The root cause of this phenomenon is unclear, and is likely multifactorial. For example, cancer-related fatigue (CRF), one of the most predominant co-morbidities in oncologic patients, has been shown to correlate with pretreatment cognitive decline, a finding backed by both clinical and neuroimaging data [13]. Psychiatric phenomena might also play a role. The prevalence of depression among patients with many solid cancers exceeds that which is observed in the general population, and cognitive complaints are a core feature in the symptomatology of depressive episodes [14] [15] [16] [17]. Similarly, post-traumatic stress disorder (pTSD) following receipt of a cancer diagnosis is another mediator of cognitive decline in some patients, albeit to a subtle degree [18] [19].

However, in addition to the impact of depression, stress, surgery, medications, age and genetics on cognitive function, evidence confirms the existence of CICD as an independent entity in cancer patients. CICD, defined as both a constellation of subjective symptoms and an empirically-diagnosable entity, impacts patients across disease sites and longitudinally throughout both their treatment and recovery. A better understanding of the risk factors and features of CICD will improve informed consent, patient education, and documentation of outcomes. It is of utmost importance to better characterize and understand this disorder in order to devise treatments that will allow us to improve quality of life for our patients.

2. Methodology

In this clinical review, a search for peer-reviewed papers from 1980 to 2019 was performed using the Ovid MEDLINE database using a combination of terms describing cognitive function, chemotherapy, and cancer therapy. In addition, a PubMed search was performed to identify recent papers not currently indexed. References were crosschecked to ensure that all relevant literature was identified and included. A total of 172 papers were reviewed encompassing all study designs, with a special focus on cross-sectional and prospective longitudinal studies evaluating post-chemotherapy cognitive deterioration. After excluding 50 papers, a total of 122 relevant studies were included in this review.

3. Chemotherapy-Induced Cognitive Dysfunction: Subjective Symptoms versus Clinical Findings

Self-Reported CICD

The subjective experience of cognitive deterioration following chemotherapy, herein "self-reported CICD" (SRCICD), first emerged as an important clinical problem during the 1990s in a series of studies based largely on patient interviews [20] [21]. Cognitive complaints included short-term memory loss, trouble concentrating, reduced mental flexibility and speed of information processing,

visual memory and even a slowing of motor function. More recent studies have found similar results including a 2007 online survey of 471 cancer patients in which 98% reported changes in cognitive abilities during or after chemotherapy and 92% reported persistent difficulties with cognitive function after five years [22]. Today, it is evident that the phenomenon, colloquially named "chemo-brain" or "chemo-fog", is experienced by patients across a variety of solid and hematologic malignancies [23]. Of note, the majority of the evidence is in breast cancer (BC) patients who tend to be young and highly functioning and may notice even mild perceived deficits which may limit the generalizability of these studies to cancer patients as a whole.

Estimates of the prevalence of SRCICD have varied substantially across studies (see **Table 2**) [24]-[33]. One systematic review of twenty-seven studies in BC patients, reported prevalence rates ranging from 21% to as high as 90%, with the most frequently reported deficits affecting the domains of memory, concentration

Table 2. Self-reported post-chemotherapy cognitive decline by domains affected.

Reference	Study Design	Exposure Group	Control Group	Measure	Memory Domain	Attention Domain	Executive Function Domain	General Cognitive Impairment (Domain-Nonspecific)
Schmidt et al. [24]	Cross-sectional	Various Solid Malignancies CH+ (n = 3108)	n/a	QLACS	Patients reporting as abnormal: 65.4%	n/a	n/a	Patient reporting as abnormal: 45.7%
Schagen et al. [25]	Cross-sectional	BC CH+ (n = 39)	BC CH− (n = 34)	5-point Likert scale	Patients reporting as abnormal: 31% (CH+) vs 6% (CH−) (p = 0.007)	Patients reporting as abnormal: 21% (CH+) vs 3% (CH−) (p = 0.022)	n/a	n/a
Downie et al. [26]	Cross-sectional	BC CH+ (n = 21)	n/a	Semi-structured interview	Patients reporting as abnormal: %95	Patients reporting as abnormal: 90%	Patients reporting as abnormal: 43%	n/a
Shilling et al. [27]	Longitudinal	BC CH+ (n = 142)	n/a	Semi-structured interview	Patients reporting as abnormal: - 71% at 6 months post-treatment - 60% at 18 months post-treatment;	Patients reporting as abnormal: - 64% at 6 months post-treatment - 42% at 18 months post-treatment	n/a	n/a
Skaali et al. [28]	Cross-sectional	TC CH+ one cycle of chemotherapy (n = 38); two or more cycles of chemotherapy (n = 53)	TC CH− (n = 31)	Semi-structured interview	Patients reporting as abnormal: - 26% (CH+) vs 7% (CH−) after one cycle of chemotherapy (p = 0.08); - 25% (CH+) vs 7% (CH−) after two or more cycles of chemotherapy (p = 0.08)	Patients reporting as abnormal: - 21% (CH+) vs 3% (CH−) after one cycle of chemotherapy (p = 0.09); - 13% (CH+) vs 3% (CH−) after two or more cycles of chemotherapy (p = 0.09)	n/a	Patients reporting as abnormal: - 29% (CH+) vs 10% (CH−) after one cycle of chemotherapy (p = 0.1); - 29% (CH+) vs 10% (CH−) after two or more cycles of chemotherapy (p = 0.1)

Continued

Janelsins et al. [29]	Longitudinal	BC CH+ (n = 580)	HC (n = 363)	10-point Likert scale; modified MD Anderson Symptom Inventory [31]	Difference in mean score(SE) trajectory between exposure and control: - From pre-treatment to post-treatment: 1.15 (0.14) (95% CI 0.88 - 1.42; p < 0.001) - From post-treatment to 6-month follow-up: 0.86 (0.14) (95% CI 0.58 - 1.13; p < 0.001)	Difference in mean score(SE) trajectory between exposure and control: - From pre-treatment to post-treatment: 0.99 (0.15) (95% CI 0.7 - 1.28; p < 0.001) - From post-treatment to 6 -month follow-up: 0.52 (0.15) (95% CI 0.22 - 0.81; p < 0.001)	Difference in mean score(SE) trajectory between exposure and control: - From pre-treatment to post-treatment: 1.24 (0.17) (95% CI 0.92 - 1.57; p < 0.001) - From post-treatment to 6-month follow-up: 0.84 (0.17) (95% CI 0.50 - 1.17; p < 0.001)	n/a
Janelsins et al. [30]	Longitudinal	BC CH+ (n = 581)	HC (n = 364)	FACT-COG	n/a	n/a	n/a	Change in mean (SD) score from pre-treatment to post-treatment: - CH+: -15.9 (30.86) (p < 0.001) - CH−: +1.4 (16.38) (p = 0.122) Change in mean (SD) score from pre-treatment to 6 – month follow-up: - CH+: −10.4 (31.41) (p < 0.001) - CH−: +1.5 (16.31) (p = 0.1)
Kohli et al. [32]	Longitudinal	Various Solid Malignancies CH+; (n = 595)	n/a*	11 – point Likert scale; modified MD Anderson Symptom Inventory [7]	Baseline = 54.5% During treatment = 81.8% 6 months post-treatment = 76.4%	Baseline = 55.9% During treatment = 85.9% 6 months post-treatment = 68.6%	n/a	n/a
Tager et al. [33]	Longitudinal	BC; CH+ (n = 61)	BC; CH− (n = 31)	5-Point Likert Scale	27% vs 32% before treatment; 43% vs 35% at 6 months post-treatment; 46% vs 31% at 6 months follow-up	n/a	n/a	n/a

*Compared to patients treated with chemotherapy + radiotherapy, and patients treated with radiotherapy alone, but not to CH− patients. Abbreviations: BC = Breast Cancer; TC= Testicular Cancer; CH+ = have received chemotherapy; CH− = have not received chemotherapy; HC = Healthy Controls; QLACS = Quality of Life in Adult Cancer Survivors questionnaire; FACT-COG: Functional Assessment of Cancer Therapy-Cognitive Function.

and executive functioning [34]. One of the largest longitudinal studies to address SRCICD was published in 2016 by Janelsin and colleagues [30]. The study com-

pared 581 BC patients (stage 1 to 3c) who have received chemotherapy with 364 non-cancer controls using the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) test pre-treatment, post-treatment and at a six-month follow-up point. In all three testing sessions, chemotherapy-treated BC patients had lower mean FACT-Cog scores compared with controls, indicating greater perceived cognitive deficit. In addition, the BC group showed an overall decline in the mean scores from pre-treatment to post-treatment, and from pre-treatment to the six-month point, whereas the scores for controls remained stable. Age, race, cognitive reserve, and a higher level of anxiety and depressive symptoms moderated this effect.

A striking illustration of the pervasiveness of SRCICD is the LIVESTRONG survey, an online survey which assessed cancer survivors' post-treatment experience in a variety of domains, including Perceived Cognitive Dysfunction (pCD) [24]. Reportable PCD symptoms included difficulties in concentration, attention span and recall, as well as the subjective experience of suffering from "chemo-brain". PCD symptoms were reported by 45.7% out of 3108 LIVESTRONG respondents harboring diagnoses of BC (29.1%), testicular cancer (9.1%), colorectal (5.8%), prostate (7.4%), head and neck (3.1%) and hematological malignancies, over half of which have undergone chemotherapy, which was significantly associated with PCD. In addition, those with depression were more likely to experience cognitive dysfunction.

Diagnosing CICD Using Neuropsychological Testing

Given the high prevalence of patient-reported cognitive complaints, substantial effort has been put into empirically diagnosing and quantifying CICD, herein called "objectively-verified CICD" (OVCICD). Reports vary significantly in terms of the proportion of patients affected and the cognitive domains involved: some studies have shown marked impairments, most commonly in the domains of memory, attention, concentration, executive function and processing speed; others show only subtle impairments or no impairments at all [35].

The lack of a uniform research methodology seems to account for these inconsistencies. Researchers have employed different study designs (mostly cross-sectional, some longitudinal), different control groups (healthy controls versus chemo-naive cancer patients), and different cut-off scores for diagnosing cognitive impairment [36] [37]. They have also timed the testing sessions differently relative to the time when chemotherapy was administered and have employed different testing batteries shown to differ in their respective sensitivity and specificity [38].

In 2011, the lack of consensus on how to investigate OVCICD compelled the International Cognitive and Cancer Task Force (ICCTF) to publish recommendations for standardizing CICD research [39]. In 2012, a meta-analysis of 17 studies looking at 807 patients evaluated neuro-psychologic testing of eight cognitive domains: attention, executive functioning, information processing, motor speed, verbal ability, verbal memory, visual memory, and visuospatial ability [40]. The analysis found that two cognitive domains: verbal and visuospatial ab-

ilities were most impacted by chemotherapy; verbal ability was worse in BC patients treated with chemotherapy compared to healthy controls, and visuospatial ability was worse compared to chemo-naïve BC patients.

More recently, in 2017 the largest meta-analysis on the matter to date further reinforced the notion that the presence or absence of OVCICD heavily depends on the type of control group used [41]. The study incorporated 2939 BC patients from seventy-two prior studies, both cross-sectional and longitudinal. In an analysis of overall as well as domain-specific cognitive impairment, patients treated with chemotherapy had lower cognitive scores compared to healthy non-cancer controls. Crucially, however, chemotherapy-treated patients performed equally compared with cancer patients not treated with chemotherapy. The analysis strongly suggests that chemotherapy is not a driving factor for cognitive decline in cancer patients, at least as it pertains to its diagnosis using neuropsychological testing.

On the other hand, in a counter argument for the direct culpability of chemotherapy, Collins and colleagues demonstrated a significant dose-response relationship between chemotherapy and objective cognitive decline in a cohort of 60 BC patients, compared to a healthy control group, and after controlling for pre-treatment cognitive baseline [42]. Dose response effect of chemotherapy was also identified in a case cohort study [20]. At two years following chemotherapy completion, cognitive impairment was found in 32% of the patients treated with high-dose chemotherapy, in 17% of the patients treated with standard-dose chemotherapy, and in 9% of the control patients. In comparison with the control patients, patients treated with high-dose chemotherapy appeared to have an 8.2-times higher risk of cognitive impairment (odds ratio; 95% confidence interval [CI] = 1.8 - 37.7); in comparison with the patients who received standard-dose chemotherapy, this risk of impairment was 3.5-times higher (95% CI = 1.0 - 12.8).

Neuroimaging

In contrast to the variable results of neuropsychological testing, imaging-based studies have produced more consistent evidence for an obvious, measurable effect of cytotoxic drugs on the brain. These neuroimaging and the correlating anatomic brain changes have also been documented in early onset dementia syndromes, which present with similar alterations in memory and executive function [43].

Prospective longitudinal magnetic-resonance imaging (MRI) studies show reductions in grey matter volume following chemotherapy [43] [44] [45] [46] [47]. These reductions, noted across multiple regions of the brain including the frontal, parietal, temporal and occipital lobes, occur early in treatment and have been demonstrated to only partially recover over time [46]. White matter changes also occur, including altered neuronal morphology, leukoencephalopathy, gliosis and demyelination [48] [49] [50] [51].

Chemotherapy not only influences the brain's *morphology* but its *hemody-*

namics as well. In a longitudinal follow-up of twenty-seven BC patients using pulsed arterial spin-labeling MRI, significantly increased cerebral perfusion was observed in the right precentral gyrus one month after completing cytotoxic treatment [52]. The authors postulated that this might reflect a compensatory hemodynamic response to treatment-induced neural damage. This increase in perfusion was negatively correlated with pre-treatment cognitive function, suggesting that lower cognitive reserve may be a risk factor for post-treatment cerebral perfusion dysregulation. Similarly, Chen and colleagues reported significant increases in cerebral blood flow across various brain regions following neoadjuvant therapy for BC which was significantly correlated with reduced performance on various attention tasks [53].

Finally, the apparent *structural* and *hemodynamic* changes induced by chemotherapy seem to coincide with *functional* alterations, as a growing number of functional MRI (fMRI) studies now show. For example, Miao *et al.* evaluated the long term chemotherapy-related functional changes to the anterior cingulate cortex (ACC) using fMRI in twenty-three chemotherapy-treated BC patients as compared to twenty-six healthy control subjects [54]. The results showed that functional connectivity was significantly lowered in the chemotherapy group and the observed changes were correlated with a reduction in executive function abilities as demonstrated in the Stroop Interference Test. Another study aimed to assess the long-term impact of cisplatin-based chemotherapy on whole-brain networks in testicular cancer patients who were recently orchiectomized [55]. Sixty-four patients underwent baseline and six-month follow-up fMRI imaging and neuro-cognitive testing. Of this cohort, twenty-two subjects were treated with cisplatin and forty-two were under surveillance only. Analysis showed that in patients who had received cisplatin, key connectivity properties of the brain were altered which affect distribution of information across the brain, both on the local as well as the global level [56]. Changes to these measures might reflect suboptimal cognitive abilities and reduced tolerability to local insult, and indeed the imaging findings correlated with poorer overall cognitive performance in the treated group.

A Chasm between SRCICD and OVCICD

Taken as a whole, the data on OVCICD reveals an obvious discrepancy between patients' subjective experience of CICD, which is often substantial and crippling, and the underwhelming neuropsychological test results. In an illuminating systematic review, Hutchinson and colleagues analyzed 24 prior studies that used objective and subjective measures *simultaneously* to diagnose CICD in the same cohort. Of the included studies, only eight reported on a significant correlation between the two measures [57]. This finding suggests that SRCICD and OVCICD might be two independent phenomena: some patients have objective cognitive decline which is too subtle to interfere with their daily lives and thus goes unnoticed and unreported; in other patients, the burden of chemotherapy creates the subjective experience of impairment without any measurable

cognitive deterioration. This self-reported overestimation of cognitive impairment is not at all unique to cancer patients. It has been documented in the context of major depressive disorder, multiple sclerosis, rheumatoid arthritis and HIV, among other conditions [58] [59] [60] [61].

Nevertheless, there is a two-fold rationale for monitoring for SRICD in the post-treatment setting. First, research performed in Alzheimer's disease and vascular dementia indicates that subjective complaints are predictive of measurable cognitive decline at a later stage [62] [63]. Secondly, discrepancies between subjective reporting and objective measurements aside, there is no denying the far-reaching implications of CICD on quality of life. Qualitative data shows that it can diminish patients' self-confidence and self-esteem, undermine their sense of independence and bring about guilt over not being able to maintain their former agency [64]. Another recurring theme is frustration due to what is perceived as lack of acknowledgment of the symptoms by spouses, family members and even the medical team [65]. Furthermore, difficulties in returning to the workplace and in maintaining performance at the necessary level might translate into serious economic impacts for patients, as well [66].

4. CICD Mechanisms

The clinical findings, as well as the functional and morphologic brain findings associated with CICD, are most likely the endpoint of multiple mechanisms acting on the brain in synergy. The three most thoroughly developed hypotheses as to the underlying causes are described below.

CICD in the Context of Accelerated Aging

It has been argued that CICD can best be understood in the broader context of chemotherapy-induced accelerated aging [67]. Evidence pointing to a hastening of the aging process brought about by cancer and/or its treatment is abundant across studies ranging from animal models to epidemiological analyses.

From a clinical standpoint, physiological frailty, which includes cognitive deterioration, can be considered a "physical phenotype" of aging [68]. Interestingly, a study conducted by Ness and colleagues in 2005 has shown frailty to be prevalent in young adult survivors of childhood cancer at a similar rate to that encountered among adults sixty-five years old and above [69]. On the molecular level, chemotherapeutic treatment has been shown to negatively affect several well-identified biological markers of aging [70]. In a recent example, Sanoff *et al.* prospectively examined the effects of cell senescence marker expression (p16INK4a, ARF mRNA) as well as senescence-associated cytokines in thirty-three women with stage 1 - 3 BC71. Data was collected at four data points: prior to receiving anthracycline-based chemotherapy, immediately upon completing chemotherapy, three months after completing chemotherapy, and finally twelve months after completion of therapy. The analysis showed that expressions of P16INK4a and ARF were elevated immediately after completing chemotherapy, and remained elevated at the twelve-month mark. Interestingly, the absolute increase in the

expression was 75% which is equivalent to the increase observed over 14.7 years of chronological aging. In addition, expression of two senescence-associated cytokines (VEGFA and MCP1) was durably increased by adjuvant chemotherapy. In a compelling pre-clinical study, Chiang *et al.* demonstrated for the first time that treatment of adult mice with cisplatin resulted in a significant increase in endogenous hippocampal clustering of the Tau protein, a phenomenon associated with cognitive decline commonly demonstrated in aging brains [71] [72].

To assert a demonstrable clinical correlation between the changes in biological markers of aging with actual symptomatic cognitive decline, Carroll and colleagues evaluated a cross-sectional cohort of 94 women treated with chemotherapy for early-stage BC in the previous 3 - 6 years [73]. The group measured the rate of leukocyte DNA damage, peripheral blood mononuclear cell (pBMC) telomere length as a marker of telomerase activity, and the level of tumor necrosis factor receptor 2 (a soluble inflammatory marker), as well as a cognitive function using neuropsychological testing and self-reporting. Higher rates of DNA damage, as well as lower telomerase activity, were related to lower executive function scores. In addition, lower telomerase activity was associated with worse attention and motor speed scores suggesting that biological markers of aging and cognitive decline are related in this chemotherapy-treated cohort.

CICD as a Result of Cytokine Dysregulation

Many cytotoxic drugs are known to cause dysregulations to the body's cytokine milieu, with significant post-treatment increases observed in the circulating levels of TNF-*α*, IL-1, IL-6, IL-8 and more [74]. An association between these serum cytokine elevations and post-chemotherapy cognitive deteriorations, both objectively measured and self-reported, has been demonstrated repeatedly in clinical studies [75] [76] [77].

The exact mechanism by which peripheral cytokines might be exerting a central negative effect in the CNS has not been elucidated, however, a recent multi-modality study in mice conducted by Shi *et al.* offers new insight on the matter [78]. Intra-peritoneal injections of docetaxel, adriamycin and cyclophosphamide were administered to healthy mice and the effect of the treatment on the CNS was examined by correlating tissue and serum cytokine levels with cognitive performance using a water maze test, neuronal activity in the hippocampus using manganese-enhanced MRI and the rate of formation and elimination of dendritic spines in the medial prefrontal cortex using transcranial two-photon microscopy. Following treatment, significant elevations in the level of both peripheral and central pro-inflammatory cytokines were recorded, alongside significant reductions in the level of anti-inflammatory cytokines. Crucially, central pro-inflammatory cytokines levels were inversely correlated with cognitive performance, as well as with hippocampal signal intensity as detected by MRI. In addition, central cytokine levels were positively correlated with a marked net loss of dendritic spines, indicating impaired neuroplasticity. This study suggests a direct effect of chemotherapy on central cytokine levels, and a possible mechan-

ism by which central cytokines might be contributing to CICD. Whether or not peripheral cytokines are also indirectly involved in this process, for example, by stimulating the production of central cytokines, as has been previously suggested, is unclear [74].

Oxidative Stress

Cytokine disruption is closely linked to another putative mechanism involved in CICD: oxidative stress. The result of an imbalance between the formation and destruction of Reactive Oxygen Species (ROS), oxidative stress has deleterious effects on multiple organ systems [79]. Perhaps most relevant to the discussion concerning CICD, it has been heavily implicated as an important contributor to the development of Alzheimer's disease [80] [81].

Approximately half of all FDA-approved chemotherapeutic drugs generate ROS, either as part of their anti-neoplastic effects or in non-targeted tissues [82]. Among them is the prototypical ROS-generating drug doxorubicin/adriamycin. Extensive research into doxorubicin implicates ROS as not only the plausible mediators of the drug's well-known dose-limiting cardiotoxicity, but also as mediators of CICD in treated cancer survivors [81] [83]. Despite being unable to cross the blood-brain barrier (BBB), doxorubicin has demonstrable neurotoxic properties in the CNS, which are mediated through oxidation of serum proteins and a subsequent elevation in circulating, as well as central levels of the pro-inflammatory cytokine TNF-α [84] [85]. A high ROS concentration has been shown to lead to a decline in cognitive functions, and is associated with some neurodegenerative disorders and age-dependent decay of neuroplasticity [86].

This mechanism might be shared by other common ROS-generating anti-neoplastic drugs such as cyclophosphamide and methotrexate [87]. It also opens the door to several potential therapeutic targets to prevent ROS-mediated CICD, for example, co-administering anti-TNF antibodies [85]. Animal experiments have shown that doxorubicin-induced oxidative stress is ameliorated by administering 2-mercaptoethan sulfonate sodium (MESNA), an anti-oxidant commonly given to patients as part of drug regimens containing cyclophosphamide or ifosfamide to prevent the occurrence of hemorrhagic cystitis [88].

5. Susceptibility to CICD

It is important to know if there are predisposing risk factors for CICD as determination of baseline susceptibility will allow better risk stratification and patient counseling and may alter decisions about treatment choices.

Pharmaco-Genetic Determinants

Several genetic polymorphisms have been singled out as possible determinants of CICD susceptibility. For example, it has been postulated that patients carrying the Apolipoprotein E (APOE) ε4 allele, which is an established risk factor for both Alzheimer's disease and PTSD, might be at increased risk for developing CICD [89]. Early reporting by Ahles *et al.* showed that long-term BC and lymphoma survivors who were treated with chemotherapy and carried the APOE ε4

allele had significantly lower performance in standardized testing for visual memory and spatial ability compared with similar survivors who did not carry the same allele [90]. In a more recent study, testicular cancer survivors who were heterozygous or homozygous for the ε4 allele and had been treated with BEP (bleomycin, etoposide, cisplatin) performed worse on cognitive tests compared to chemotherapy-treated patients who did not carry the allele [47].

Another avenue of investigation concerns genetic polymorphism which might render the CNS more vulnerable to penetration by intra-venously administered neurotoxic drugs which normally cannot cross into the CNS due to BBB impenetrability [91]. This impermeability to cytotoxic drugs is dependent upon the functioning of local drug transporters, chief among them the P-glycoprotein (p-gp) efflux transporter and the OATP1A2 influx pump [92] [93]. Since many commonly used anti-neoplastic drugs are known substrates of P-gp and OATP1A2, it has been posited that polymorphisms in the genes encoding for these transporters (ABCB1 and SLCO1A2, respectively) might play a role in an individual's susceptibility to CICD [89]. Studies exploring the association between ABCB1 single-nucleotide polymorphisms (SNPs) and chemotherapy induced toxicity have been conflicting, and few studies included CNS toxicity and/or cognitive impairment in their assessments [94]. Of note is a single study by Erdilyi *et al.* who retrospectively assessed the correlation between chemotherapy-associated encephalopathy and ABCB1 genotypes in 291 acute lymphoblastic leukemia patients [95]. The genotypes of an additional gene in the same ATP-binding cassette transporter family of genes, ABCG2, were also examined. The authors showed that carrying the ABCB1 3435 TT genotype confers a higher risk of treatment-induced encephalopathy, while carrying both a mutated ABCB1 and a mutated ABCG2 allele results in an even higher risk, suggesting a synergistic effect of the two polymorphisms together. Whether this finding is generalizable to the realm of CICD remains debatable, as there are multiple mutations and genetic polymorphisms in this gene family and further investigation is necessary [96].

Baseline Cognition as a Potential Moderator of CICD

Cognitive reserve is known to be neuroprotective, as demonstrated by the enhanced recovery from traumatic brain injury and in the slowed trajectory of neurodegenerative disease [97] [98]. It is intuitive to thus assume that a more robust cognitive reserve prior to adjuvant treatment might serve to attenuate OVCICD, however clinical data on this potential effect is lacking. To this end, Ahles *et al.* longitudinally assessed sixty BC patients with a standardized neuropsychological testing battery before commencing chemotherapy and later at three additional intervals [99]. The researchers found a three-way interaction between receipt of chemotherapy, pre-treatment cognitive reserve (assessed using the proxy of reading ability measured via the Wide Range Achievement Test) and patient age, such that older patients with lower baseline reserve demonstrated impairments to the processing speed domain not exhibited in

the various control groups (healthy controls, younger patients, chemo-naïve patients).

With regards to a similar interaction between cognitive reserve and SRCICD, the opposite could be expected, namely that well-educated patients with occupations requiring high-level functioning might be more sensitive to even the slightest cognitive changes and thus more likely to report on cognitive symptoms. Interestingly, however, limited evidence suggests that increased cognitive reserve attenuates the subjective perception of CICD [30]. In a longitudinal study using the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) questionnaire, Janelsins and colleagues found that decreased reserve prior to chemotherapy significantly correlates with lower FACT-Cog scores in BC patients [30]. Similar to the previous study by Ahles *et al.*, baseline reserve was assessed through the proxy of reading ability, using the Wide Range Achievement Test (WRAT) [99].

6. Future Areas of Investigation

With the development of targeted chemotherapeutic agents, the potential for novel drug classes to contribute to or worsen chemotherapy induced cognitive dysfunction is real. Emerging therapies such as immunotherapies and targeted therapies will need to be studied to identify any cognitive side-effects in treated patients. Additionally, several pharmacologic and nonpharmacologic interventions have been evaluated as potential therapies for cognitive decline and CICD which may be used as adjuncts during conventional chemotherapeutic treatment.

Emerging CICD Culprits

Of novel cancer therapies, perhaps the most attention should be paid to immune check point inhibitors (ICIs) for two reasons: first, immune checkpoint blockade is dramatically changing the management of certain malignancies with clinical usage rapidly increasing in these populations; and second, novel severe immune-related adverse events (IrAEs) have already been described in many organs including the CNS after treatment with ICIs, with sometimes fatal results [100] [101].

In one single institution series, 2.4% of all patients treated with ICIs developed a neurological IrAE, a rate similar to previous reports [101] [102] [103]. Notably, the rate of neurological IrAEs reached 14% in patients treated with the common regimen of ipilimumab plus nivolumab. However, cognitive dysfunction was not an endpoint of this study and thus how CNS effects from these medications may impact cognition is still unknown and a paucity of additional data exists to guide clinicians. McGinnis *et al.* showed in their 2017 study that mice treated with a combination of anti-CTLA4 antibody plus CT-guided peripheral irradiation showed impairments in object recognition following treatment [104]. In the clinical setting, Cuzzubbo *et al.* performed a small-scale feasibility study in which fifteen non-small cell lung cancer and melanoma patients were neurologically assessed prior to commencing ICI treatment (ipilimumab, nivolumab or pembrolizumab)

and again 3 months later [105]. Performance in two neuropsychological tests (MoCA and TNI-93) remained stable or improved at the three-month mark, with no evidence of cognitive dysfunction due to the treatment in any of the patients. However, further larger-scale prospective studies will be required in order to determine whether or not ICIs exert any influence on cognition. One methodological challenge in future studies will be controlling for the effects of chemotherapy, since many patients exposed to immune checkpoint blockade would have already been treated with often multiple lines of cytotoxic chemotherapy.

Interventions for CICD Prevention and Treatment

There are currently no FDA-approved drugs for the prevention or treatment of CICD, and no quality data to support the endorsement of any such interventions. However, preliminary clinical and pre-clinic studies have shown promising results, which, at a minimum, should encourage further investigation (see Table 3).

Table 3. CICD interventions under investigation.

Pharmacologic Interventions, Pre-Clinical Studies			
Reference	**Intervention Investigated**	**Animal Model**	**Findings**
Tangpong et al. [85]	Anti-TNF antibody	Mice treated with systemic doxorubicin (intraperitoneal injection) with/without anti-TNF antibody	- TNF levels in brain tissue were significantly elevated following doxorubicin treatment ($p < 0.01$) - Measures of brain mitochondrial function were significantly reduced following doxorubicin treatment ($p < 0.05$) - Anti-TNF antibody administration prevented the increase of central TNF levels, as well as the decline in mitochondrial function
Keeney et al. [88]	2-mercaptoethanesulfonate sodium (MESNA)	Mice treated with systemic doxorubicin (intraperitoneal injection) with/without MESNA	- Indicators of oxidative stress (protein carbonyl, protein-bound 4-hydroxynonenal) were significantly elevated in the sera and brain tissue of mice following doxorubicin administration (*brain*: $p < 0.01$; *sera*: $p < 0.0001$ *for protein carbonyl*, $p < 0.001$ *for protein-bound* 4*-hydroxynonenal*) - Novel Object Recognition (NOR) was significantly reduced in doxorubicin-treated mice ($p < 0.05$) - MESNA administration before and after doxorubicin ameliorated the rise of oxidative stress measures in brain ($p < 0.01$) and sera ($p < 0.01$ *for protein carbonyl*, $p < 0.05$ *for protein-bound* 4*-hydroxynonenal*) - MESNA administration prevented the doxorubicin-induced deterioration in NOR
Zhou et al. [106]	Metformin	Mice intra-peritoneally treated with cisplatin with/without metformin	- Exposure to cisplatin significantly reduced performance in the Novel Object and Place Recognition Test (NOPRT) ($p < 0.05$), an effect that was not exhibited in subjects treated concurrently with metformin

Continued

Chiu et al. [107]		Mesenchymal stem cells (MSC)	Mice intra-peritoneally treated with cisplatin, followed by intra-nasal administration of MSC	- Cisplatin treatment caused deteriorations in executive function, spatial memory and working memory, as measured via the puzzle box test (pBT), the NPORT and the Y-maze test, respectively ($p < 0.05$). - Intra-nasal administration of MSC normalized performance levels in the above-described cognitive tests.

Pharmacologic Interventions, Clinical Studies

Reference	Study Design	Intervention Investigated	Study Population	Findings
Lawrence et al. [111]	Randomized, placebo-controlled pilot study	donepezil	BC patients (n = 47) 1 - 5 years following receipt of adjuvant chemotherapy (>4 cycles)	- Patients receiving daily donepezil (5 mg PO for 6 weeks, followed by 10mg PO for an additional 18 weeks) performed significantly better than placebo in two memory parameters of the Hopkins Verbal Learning Test Revised: Total Recall ($p = 0.033$) and Discrimination ($p = 0.036$).
Kohli et al. [112]	Open-label followed by placebo-controlled randomization	modafinil	BC patients (n = 68) who had previously received chemotherapy and/or radiotherapy and have reported symptoms of Chemotherapy-Related Fatigue (CRF)	- Phase 1 (open-label): patients who have received modafinil 200 mg PO once daily for 4 weeks in an open-label fashion demonstrated significant improvements in speed of memory ($p = 0.0073$) and episodic memory ($p < 0.0001$) compared to baseline. No effect was observed in the domains of attention ($p = 0.0568$) and working memory ($p = 0.2475$). - Phase 2 (randomized): patients randomized to modafinil showed greater improvements in speed of memory ($p = 0.029$), episodic memory ($p = 0.0151$) and continuity of attention ($p = 0.0101$) compared to placebo.
Lundorff et al. [113]	Double-blind, randomized, cross-over trial	modafinil	Patients with various advanced solid malignancies (n = 36), and a tiredness score of >50 mm on the Edmonton Symptoms Assessment System (ESAS).*	- Modafinil elicited significantly superior results compared with placebo in two cognitive tests: Finger Tapping Test (FTT) for evaluation of psychomotor speed ($p = 0.006$) and the Trail Making Test (TST) of visual attention and task switching ($p = 0.042$)
Blackhall et al. [114]	Open-label pilot study	modafinil	26 cancer patients (types unspecified) with a Brief Fatigue Inventory (BFI) score of at least 4*	- After completing a four-week course of oral modafinil (100 mg daily for two weeks, followed by 200 mg daily for an additional two weeks), patients showed no significant change in performance on the following neurocognitive tests: the Hopkins Verbal Learning Test (HVLT), the Grooved Pegboard Test, the Controlled Oral Word Association Test (COWAT) and the Trail Making Test A.
Berenson et al. [115]	Double-blind, placebo controlled phase three trial	armodafinil**	Multiple myeloma patients (n = 35) with moderate CRF*	- Patient receiving oral modafinil (150 mg daily for 56 days) showed no significant improvement compared to placebo in three objective measures of cognitive function (the Trail Making Test-version B, the Symbols Digits Modality Test and the digit span test)
Escalante et al. [117]	Randomized, double blind, placebo-controlled crossover trial	methylphenidate	BC patients (n = 38), 35 (92.1%) of which were undergoing chemotherapy or chemotherapy + ET treatment during the study period	- Methylphenidate-treated patients (18 mg/day for two weeks) performed significantly better than placebo in the Wechsler Adult Intelligence Scale Digit Span Test ($p = 0.001$), indicating improved cognitive processing speed.

Continued

		Behavioral Interventions		
Reich et al. [119]	Randomized, controlled trial	Mindfulness-Based Stress Reduction (MBSR)	BC patients (n = 322), 35.7% of which have received chemotherapy + radiotherapy	- Immediately following a six-week MBSR program, no significant change was observed in cognitive performance compared with usual care, as measured by the Everyday Cognition scale (ECog)
Dobos et al. [120]	Prospective single-arm cohort study	Mindfulness-Based Stress Reduction (MBSR)	Cancer patients (n = 117), of which 65% were diagnosed with BC and 48.72% had received chemotherapy.	- Immediately following an eleven-week MBSR program, significant improvement was observed in the cognitive subset of the European organization for research and treatment of cancer quality of life questionnaire (EORTC QLQ-C30). (p = 0.001) - Results were sustained at the three-month follow up period (p = 0.001)
Fernandes et al. [122]	Systematic review of 19 studies (12 randomized controlled trials, 3 non-randomized controlled trials, 4 single arm studies).	Cognitive rehabilitation	Patients with various solid and hematological malignancies; 11 studies recruited only BC patients; BC was the most common diagnosis across all studies. The vast majority of BC patients had received prior chemotherapy.	- All included studies found significant improvement in at least one cognitive domain following a cognitive rehabilitation intervention, either objectively-assessed or self-reported. - Objective improvement in memory was the most frequently reported finding.
Oberste et al. [124]	Single-blinded randomized controlled trial ***	High Intensity Interval Endurance Training (HIIT)	BC patients (n = 59) currently undergoing first-line chemotherapy, concurrently with a HIIT program or a placebo program (myofascial release training)	- Change in cognitive performance from baseline to the end of the HIIT intervention will be assessed using the Hopkins Verbal Learning Test, Controlled Oral Word Association Test and the Trail-Making-Test

*No information regarding prior chemotherapy treatment; **Armodafinil is a levorotatory enantiomer of modafinil; ***Ongoing study, results pending. Abbreviations: BC: breast cancer; CRF: cancer-related fatigue; MESNA: 2-mercaptoethanesulfonate sodium (MESNA); MSC: mesenchymal stem cells; MBSR: Mindfulness-Based Stress Reduction; HIIT: High-Intensity Interval Training.

Pre-Clinical Studies

As mentioned above, researchers have shown that both anti-TNF antibodies as well as 2-mercaptoethan sulfonate sodium (MESNA) ameliorate the oxidative damage caused by doxorubicin treatment in animal models [85] [88]. In 2016, a group at the MD Anderson Cancer Center used the anti-diabetic drug metformin in mice to successfully prevent cisplatin-induced cognitive deficits in spatial orientation, memory and social discrimination [106]. The drug, which was co-administered together with cisplatin, also helped prevent cisplatin-related morphological abnormalities in the animals' brains, as well as the occurrence of cisplatin-induced peripheral neuropathy. At the same center, a different group using the same cisplatin-induced CICD mouse model demonstrated similar results using nasally-administered mesenchymal stem cells [107]. Stem cell treatment improved cognitive performance related to executive function, spatial recognition and working memory and also reversed a cisplatin-associated decrease in functional neuronal connectivity observed using fMRI.

Most recently, Philpot *et al.* reported that cyclophosphamide and doxorubicin-induced spatial memory deficits in mice were successfully prevented by

co-administering the acetylcholine esterase inhibitors donepezil and galantamine together with chemotherapy [108]. Interestingly, the administration of the same drugs after completion of chemotherapy did not prevent the development of these deficits in a separate mice cohort.

Clinical Studies

Extrapolating from experience with Alzheimer's disease, donepezil has also been evaluated in the clinical setting [109]. In Phase 3, randomized placebo-controlled trial among brain tumor survivors who received radiation, administration of donepezil did not improve patients' overall cognitive scores but did elicit a modest benefit in the domains of memory, dexterity and motor speed [110]. In a pilot study of BC survivors who received prior chemotherapy, daily 5 - 10 mg of oral donepezil improved patients' performance on two memory tests as compared to controls. However, no improvement was demonstrated in other cognitive domains or in self-reporting of cognitive functions [111]. Given this conflicting evidence, further phase 3 trials are required to elucidate the potential role of anti-cholinergic medications in countering CICD symptoms.

Another agent under investigation is modafinil, routinely used as a first-line pharmacologic treatment for narcolepsy-associated daytime sleepiness. In cancer patients, there is some limited evidence for cognitive improvement with modafinil therapy [112] [113]. Kohli *et al.* administered 200 mg of oral modafinil daily to 76 previously treated BC patients in an open-label fashion for a period of 4 weeks. Patients with a positive cognitive response as demonstrated by improved memory and attention tests were then randomized to either continuation of modafinil for an additional 4 weeks or placebo. At the completion of the second phase of the study, modafinil was found to significantly improve memory and attention skills compared to placebo [112]. A separate trial evaluated modafinil in the palliative setting for 28 patients with advanced cancer and a high tiredness score. The drug evoked superior performance compared with placebo in two cognitive tests: the Finger Tapping Test (FTT) for evaluation of psychomotor speed, and the Trail Making Test (TST) for assessing visual attention and task switching [113]. Conversely, evaluations of modafinil for cognitive dysfunction as a secondary outcome in two studies of cancer-related fatigue (CRF) found no improvement in any of the administered cognitive tests after treatment [114] [115]. A recent meta-analysis of 19 placebo-controlled trials in non-sleep-deprived adults showed only limited ability of modafinil to improve cognition outside the already established setting of sleep-deprivation [116].

Finally, in 2014, a randomized placebo-controlled crossover trial evaluated the effect of methylphenidate on cognitive performance as a secondary outcome among 33 women with BC undergoing chemotherapy [117]. CRF, the primary endpoint of the study, was not improved by the intervention, however, treated patients performed better on tests of memory, scanning speed, verbal learning and visual perception, suggesting a potential role for methylphenidate in alleviating CICD.

Non-Pharmacological Interventions

Given the dearth of effective pharmacologic treatments, there has been significant interest in developing *behavioral* interventions to treat CICD. Efforts to apply mindfulness-based interventions to the problem of CICD has produced some evidence of benefit, however, results across studies are conflicting [118] [119] [120]. Cognitive rehabilitation strategies, aimed at restoring damaged cognitive skills through re-training and the development of compensatory mechanisms, have also been examined, beginning with a pilot study in 2007 which showed initial promise for reversing changes in attention and memory [121]. Encouragingly, 18 subsequent studies including 12 randomized-controlled-trials, showed improvement in at least one cognitive domain after implementing cognitive rehabilitation for CICD patients [121] [122]. Finally, following initial positive results in an animal model, two clinical trials are currently underway investigating the impact of aerobic physical exercise and High-Intensity Interval Training (HIIT) on CICD in patients with acute myeloid leukemia and BC, respectively [123] [124] [125].

7. Conclusion

Taken together, the evidence confirms the existence of CICD as a substantial, albeit subtle, clinical issue for cancer patients. However, it is important to rule out other potential causes of cognitive dysfunction. While formal neurocognitive testing might not be sensitive enough to detect CICD, the impact on patients' quality of life is unmistakable and we believe that this merits the inclusion of CICD in any pre-treatment consent discussion in the same way as other better-established risks of chemotherapy. In aiming to improve the quality of life for cancer survivors, we see a need for better measures in two key fields: identifying who is most at risk of developing CICD, and screening for early signs of cognitive deterioration. A third field-prompt intervention is still lacking in actionable data and requires further rigorous investigation.

Conflicts of Interest

The authors have no disclosures or conflicts of interest.

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Abbreviations

ACC—Anterior Cingulate Cortex
APOE—Apolipoprotienε4 Allele
BBB—Blood-Brain Barrier
BC—Breast Cancer
BEP—Bleomycin, Etoposide, Cisplatin
CH+—Cancer Patients Receiving Chemotherapy
CH−—Cancer Patients Not Receiving Chemotherapy
CICD—Chemotherapy Induced Cognitive Dysfunction
CRF—Cancer-Related Fatigue
Dox—Doxorubicin
ET—Endocrine Therapy
FACT-Cog—Functional Assessment of Cancer Therapy-Cognitive Function
FMRI—Functional Magnetic Resonance Imaging
GMV—Grey Matter Volume
HC—Healthy Non-Cancer Controls
ICCTF—International Cognitive and Cancer Task Force
ICI—Immune Check Point Inhibitor
MESNA—2-Mercaptoethan Sulfonate Sodium
MRI—Magnetic Resonance Imaging
OV-CICD—Objectively-Verified Chemotherapy Induced Cognitive Dysfunction
PBMC—Peripheral Blood Mononuclear Cell
PCD—Perceived Cognitive Dysfunction
SR-CICD—Self-Reported Chemotherapy Induced Cognitive Dysfunction
ROS—Reactive Oxygen Species
TC—Testicular Cancer