REVIEW

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Chemotherapy-related cognitive impairment and kidney dysfunction

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ABSTRACT

Cancer and kidney diseases (KD) intersect in many ways resulting in worse outcomes. Both conditions are correlated with cognitive impairment, which can be exacerbated in cancer patients by known effects of many antineoplastic drugs on cognition, leading to a phenomenon known as chemotherapy-related cognitive impairment (CRCI). This manifests as poor attention span, disturbed short-term memory, and general mental sluggishness. This literature review explores CRCI and investigates the potential impact of KD on this phenomenon. Additionally, we highlight the shared pathogenetic mechanisms (including neurotoxicity, neuroinflammation, oxidative stress, vascular disease, electrolyte, and acid-base imbalances), clinical presentation and imaging findings between cognitive impairment in KD and CRCI. The disruption of the blood–brain barrier might be a key mechanism for increased brain permeability to anticancer drugs in nephropathic patients with cancer. Based on existing knowledge, we found a potential for heightened neurotoxicity of antineoplastic drugs and a synergistic potentiation of cognitive impairment in cancer patients with KD. However, further translational research is urgently required to validate this hypothesis.

Keywords: anticancer drugs, blood–brain barrier, chemotherapy-related cognitive impairment, chronic kidney disease, neurotoxicity

INTRODUCTION

Onco-nephrology is an emerging field in medicine, gaining importance due to the intricate bidirectional relationships between cancer and kidney function. Nephrologists and oncologists face challenges in caring for an increasingly complex patient population [1]. Cancer can adversely affect kidney function through various mechanisms, such as nephrotoxicity from anticancer treatments, cancer-related glomerulopathies, increased exposure to nephrotoxic contrast media, nutritional status decline, urinary tract obstruction, and tumor-lysis syndrome. Conversely, kidney complications adversely impact survival and hospitalization rates in cancer patients [2]. Kidney function decline can occur at any stage of cancer, leading to increased mortality and hospitalization rates [3, 4]. Together cancer and kidney diseases (KD) have a substantial impact on quality of life [5, 6] due to common symptoms like fatigue, pain, sleep disturbances, cognitive deficits, and depression. Cognitive impairment (CI) has been observed in both cancer and KD. However, the inhomogeneity of clinical studies prevents drawing a clear epidemiological causality. CI is commonly reported in patients with cancer during and after undergoing chemotherapy for a range of cancer types including breast, colorectal, lung, prostate, and ovarian cancers. This phenomenon, known as chemotherapy-related cognitive impairment (CRCI; named 'chemobrain' or 'chemofog' in the lay press) can include acute or long-term impairment of executive function,

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learning, memory, processing speed, and other cognitive domains [7]. CRCI has been linked to a variety of chemotherapy regimens but is well documented in breast cancer survivors who have been treated with the antineoplastic antibiotic doxorubicin alone or in combination with other chemotherapeutic agents [7]. The mechanisms underlying CRCI are still not well defined, and the kidney function of such patients has not been reported. However, mechanisms of CRCI include direct neurotoxicity through disruption of the blood–brain barrier (BBB), decreased neuronal growth and increased apoptosis, white matter abnormalities, alterations of long-term potentiation, oxidative stress, immune dysregulation or an increased inflammatory response, alterations in cerebral blood flow and blood vessel density, hormonal changes, and electrolyte and acid base imbalances, as well as potential cognitive impairment induced by the cancer itself [7, 8]. Many of the same mechanisms have also been correlated with CI in KD [9]. However, the cognitive performance of cancer patients with KD receiving anticancer therapies, remains largely unexplored. To provide an informative insight into this topic, our narrative literature review will discuss various facets of CRCI and explore the potential influence of KD on the onset and severity of CRCI in cancer patients with kidney comorbidity.

CRCI: EPIDEMIOLOGY, CLINICAL PRESENTATION, AND OTHER FACTORS

Due to the significant progress made in cancer screening and treatment in recent decades, the number of cancer survivors is increasing, and attention has shifted from pure survival outcomes to long-term consequences of cancer and cancer-related therapies. Given the aging cancer patient population and the nephrotoxicity associated with novel anticancer agents, there is also growing interest in comorbidities, such as KD.

Cognition is affected in a significant number of cancer patients undergoing chemotherapy for extra-cerebral tumors and despite the absence of brain metastases [10–22]. Prevalence rates of CRCI vary widely, but several analyses estimate roughly 75% of patients can experience CRCI during anticancer treatment, and up to 35% continue to have cognitive issues months or even years after treatment [23, 24]. There are several contributing factors, including patient-related baseline factors (e.g. age, education, comorbidities), cancer-related factors (e.g. psychological, anemia) or treatment-related factors (e.g. hormonal therapy, antiemetic treatment, toxicities in other than nervous system organs). However, most of the longitudinal studies comprising treated groups as well as control groups of healthy individuals and cancer patients without chemotherapy confirm the role of chemotherapy in the development of neurocognitive deficits [25]. In Table 1, examples of clinical studies reporting CRCI are summarized.

CRCI is characterized by cognitive deficits that may arise during or shortly after completion of chemotherapy and may be long-lasting or permanent [26]. High-functioning individuals or those with demanding professions may notice neurocognitive decline earlier [27]. Although their formal test scores might remain high, they could subjectively report cognitive difficulties and exhibit scores lower than their baseline testing. Clinically, cognitive functions—such as executive functions, verbal memory, visuospatial skills, processing speed, and attention—have been found to be affected in a manner similar to those reported in patients with KD [27, 28] (Fig. 1). Non-modifiable patient characteristics, including age, cognitive reserve, comorbidities, and genetic predisposition, influence susceptibility to CRCI. For examples, pre-existing cognitive problems related to vascular diseases, such as CKD, diabetes, and hypertension, can also exacerbate CRCI [29]. Hyperkalemia hyponatremia and metabolic acidosis commonly occur in both cancer and KD patients, and these imbalances have also been associated with poorer cognition [30–32]. In addition, there are genes, particularly apolipoprotein E (APOE 4) and catechol-O-methyltransferase (COMT), known to increase the risk of developing CI [33]. Other genes related to neural repair, plasticity, DNA damage and repair, and inflammation are also implicated. Several inherited KD, also associated with CI, show an increased neoplastic risk [34] or can be comorbid to cancer, and patients with these diseases undergoing chemotherapy might have a further deterioration of their cognitive performance.

Other patient factors that can contribute to CRCI include sleep quality, psychiatric disorders, pain medications, and other concomitant therapies. Sleep disturbances and psychological factors are common among both cancer patients and those with KD, and can significantly impact cognition. Poor sleep can impair cognitive function during waking hours [35]. Chemotherapy and hormonal changes can affect sleep quality, which is essential for attentiveness and memory consolidation [36]. Depression and anxiety, prevalent among both cancer and nephropathic patients, also play a crucial role in cognitive impairment, affecting memory and overall cognitive function [35]. In addition, pain and analgesic drugs such as opioids can severely affect cognitive performance [37]. Other analgesic drugs with nephrotoxic potential such as nonsteroidal anti-inflammatory drugs may affect cognition by inducing AKI-related cognitive impairment [38]. Corticosteroids, commonly prescribed to cancer patients and chemotherapy-related kidney complications [39], can also affect cognition and sleep, further exacerbating cognitive issues [29].

POTENTIAL LINKS BETWEEN CRCI AND KD

A plethora of kidney problems can be found in cancer patients [40], which can complicate the therapy for any underlying malignancy. Cancer patients with KD might be at a higher risk of developing severe CRCI: metabolic derangements, uremic-toxins-related neurotoxicity, electrolytes imbalances, anemia and reduced oxygen delivery to the brain are in fact contributors to CI [8].

Neurotoxicity of antineoplastic agents and the potential synergy with KD

Neurotoxicity, including neuroinflammation, oxidative stress, cellular metabolism, and mitochondrial dysfunction have been documented in both humans and animal models following chemotherapy administration, and are also widely reported in KD. Effects on numerous neuroinflammatory markers, including nitrate, advanced oxidation protein products (AOPP), CD68, chemokine (C-C motif) ligand (CCL) 3, CCL4 and CCL11, cyloxygenase-2 (COX-2), endothelin-1 (ED-1), granulocyte macrophage-colony stimulating factor (GM-CSF), IFNγ, IL-1β, IL-4, IL-6, IL-10, IL-12p70, monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-α (TNF-α) [41] have been associated not only with several kidney side effects of chemotherapy but also with CRCI, sleep disorders, peripheral neuropathy, neuropathic pain, allodynia, and hyperalgesia [24, 41–43].

Although most chemotherapeutic agents cannot innately cross the BBB, inflammation and oxidative stress can increase BBB permeability allowing these drugs to pass through, potentially causing neurodegeneration and CRCI [44]. Several chemotherapeutic

Table 1: The table summarizes clinical study data on cancer patients who developed CRCI.

Cancer type	Cancer treatment	Study design	Sample size (n pts)	Prevalence of CRCI	Clinical/Imaging findings	Reference
Breast	5-fluorouracil, adriamycin, and cyclophosphomide-only (FAC) or FAC and paclitaxel	Experimental	37	65% acute; 61% late	↓ learning and memory ↓ executive function ↓ processing speed ↓ attention	Wefel *et al.*, 2010 [12]
Breast	Miscellaneous chemotherapy: 6 regimens reported Hormone therapy: tamoxifen, anastrozole, or raloxifene Radiation therapy	Observational	55	Not reported	↓ processing speed in older patients ↓ verbal ability ↑ self-reported cognitive symptoms	Ahles *et al.*, 2010 [13]
Colorectal	Miscellaneous chemotherapy: oxaliplatin or 5-FU Chemoradiation: irinotecan or others	Observational	227	32%	↓ processing speed, verbal learning and memory, and attention and working memory domains with CRC alone ↑ perceived cognitive impairment after chemotherapy	Vardy *et al.*, 2015 [22]
Gastrointestinal	Miscellaneous chemotherapy: 5-FU + oxaliplatin, gemcitabine + abraxane, 5-FU + irinotecan + oxaliplatin, others	Observational	218	27.5%	↑ perceived cognitive impairment	Fowler *et al.*, 2024 [20]
Gynecological	Miscellaneous chemotherapy: unspecified	Observational	73	Not reported	↑ perceived cognitive impairment ↓ QOL (role and emotional functioning)	De Rosa *et al.*, 2021 [21]
Head and neck	Radiation therapy only or with cisplatin (3 cycles)	Observational	10	90%	↓ attention, memory, processing speed, language, and executive function	Gan *et al.*, 2011 [15]
Leukemia	Tyrosine-kinase inhibitors	Observational	90	40%	↓ global neuropsychological function, verbal memory, visual attention ↑ perceived cognitive impairment	Hyland *et al.*, 2022 [14]
Lung (small and non-small cell)	Cisplatin- or carboplatin-based	Observational	28	39%	↓ visuospatial ↓ verbal fluency ↓ gray matter density and white matter integrity in paralimbic regions	Simó *et al.*, 2015 [16]
Lung (non-small cell)	Miscellaneous chemotherapy Radiation therapy Immunotherapy	Observational	33	41% subjective; 11% objective	↓ verbal memory ↓ executive functioning.	van der Weijst *et al.*, 2022 [17]
Prostate	Androgen deprivation therapy: bicalutamide followed by goserelin or leuprolide	Observational	15	Not reported	↑ reaction time on memory and executive control tasks ↓ white matter integrity (incl. corpus collosum and thalamic region)	Chaudhary *et al.*, 2022 [18]
Prostate	Androgen deprivation therapy with or without chemotherapy (docetaxel, cabazitaxel, or carboplatin/etoposide)	Observational	51	92% single test 17–26% cross-test	↓ visuomotor processing speed ↓ verbal fluency	Ihrig *et al.*, 2023 [19]

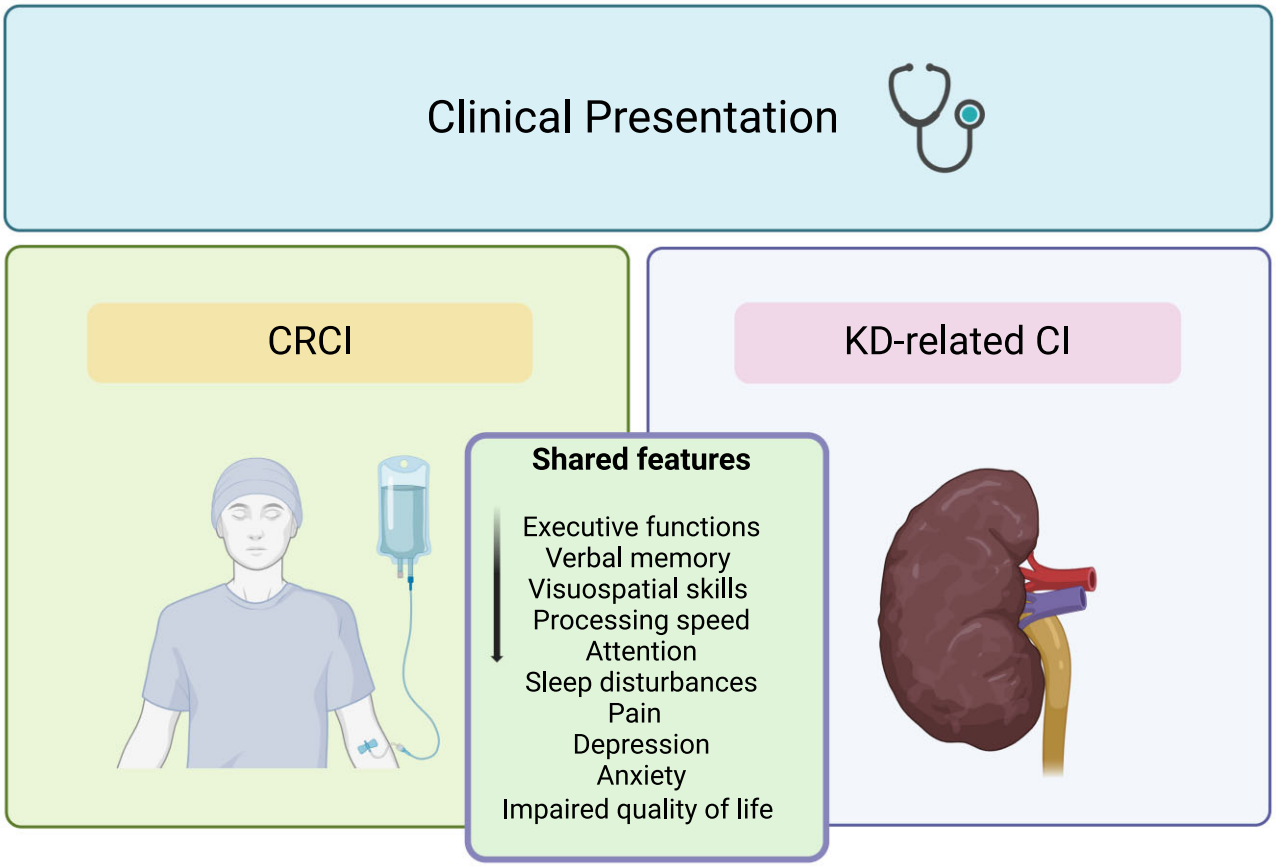

Figure 1: The figure highlights the shared clinical features of CRCI and KD-related CI. Created in BioRender. Hafez, G. (2024). https://BioRender.com/s43o058.

agents (e.g. 5-FU and tyrosine-kinase inhibitors) are able to induce cytokine-related BBB disruption associated with neuroinflammation, oxidative stress, and neurotoxicity [45]. Many chemotherapeutics act as reactive oxygen species (ROS)-generating agents and cause oxidative stress in the periphery. Malondialdehyde and glutathione are significant in identifying oxidative damage and antioxidant pathways [46–48]. The resulting oxidative stress leads to protein and lipid oxidation, increased TNF-α, and impaired BBB permeability by ROS-associated expression of the tight junction proteins and activation of the matrix metalloproteinases [49]. With the impaired BBB integrity, the increase of TNF-α and other pro-inflammatory cytokines in the brain leads to the activation of microglia. Activated astrocytes and microglial cells produce inflammatory cytokines, resulting in elevated TNF-α and NF-κB, which again leads to oxidative stress [50]. Since chemotherapy also reduces antioxidant enzymes, oxidative stress becomes more pronounced [51].

Furthermore, enhanced oxidative stress mediators, and pro-inflammatory cytokines levels and a decrease in brain-derived neurotrophic factor cause a decrease in neurogenesis and neuroplasticity and induce neuroinflammation [52]. As a result, neuroinflammation and oxidative stress interact, causing neuronal death and brain damage, particularly in the hippocampus and prefrontal cortex, key regions for cognitive function. Endothelial damage, decreased cerebral blood flow, and disruption of the neurovascular unit are among the underlying causes of CI [53]. The other neuropathological changes of CRCI include changes in neurotransmitters (acetylcholine, serotonin, dopamine, noradkidneyine, and glutamate) levels, mitochondrial dysfunction, and consequently DNA damage and inactivation of the DNA repair system [54]. All aforementioned effects might be synergistically potentiated by the pre-existence or occurrence of KD, as KD is also associated with neuroinflammation, oxidative stress, and vascular damage that are mostly triggered by shared mechanisms [43]. In addition, neurotoxic uremic toxins, especially those with exalted production by the dysbiotic gut microbiota in CKD [55] have also been reported to disrupt the BBB [56]. This CKD-related mechanism, along with the others, might further contribute to increase the brain permeability to chemotherapeutics.

Ultimately, the etiology of CRCI is complex and results from an interplay of genetic predisposition, direct neurotoxic effects, neuroinflammation, oxidative stress, vascular alterations, and comorbidities. Among the latter, KD stands out as particularly intriguing due to the shared underlying mechanisms that could act synergistically with chemotherapeutics in disrupting the cognition of cancer patients with kidney dysfunctions.

Importance of correct chemotherapy dosing on kidney function

In addition to the well-known nephrotoxic potential of various anticancer drugs, impaired kidney function per se may affect their overall toxicity and capability to induce CRCI. Different chemotherapy drugs have varied impacts that can be potentiated by their accumulation in patients with KD due to incorrect dosing or AKI occurrence. The precise dosing of chemotherapeutic agents is imperative to achieve optimal outcomes while also mitigating the risk of toxicity [57]. In this complex scenario, kidney

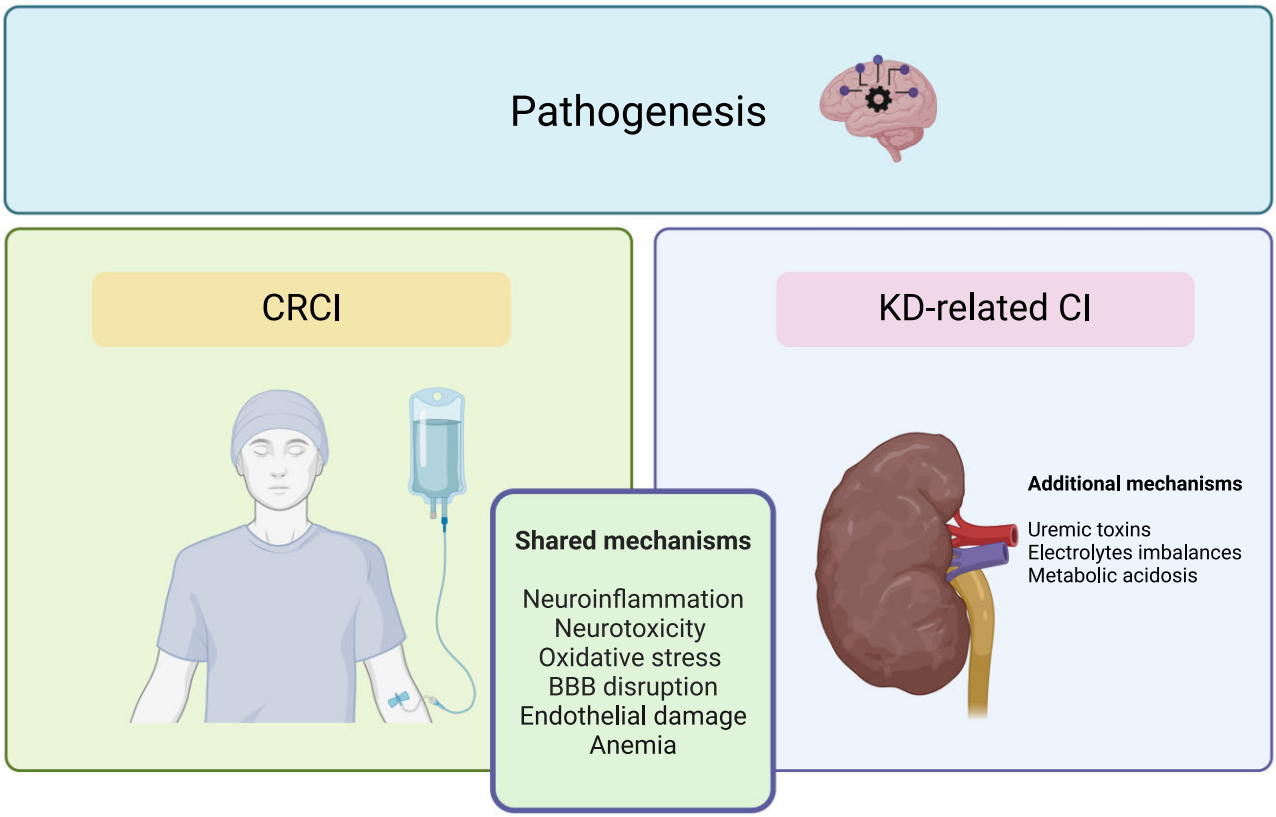

Figure 2: The figure illustrates the common pathogenetic mechanisms of CRCI and KD-related CI, while also identifying additional KD factors contributing to cognitive decline. Created in BioRender. Hafez, G. (2024) https://BioRender.com/p20v902.

function plays a dual and crucial role as both a cause and effect, serving as key factor in determining accurate chemotherapeutic dosing as well as being influenced by the nephrotoxicity of these treatments.

Chemotherapeutic agents generally have a narrow therapeutic index [58], and agents with kidney excretion ≥30% include members of several drug classes such as alkylating agents (e.g. platinum compounds, ifosfamide, carmustin, melphalan), antimetabolites (e.g. methotrexate, fludarabin, pemetrexed), topoisomerase inhibitors (e.g. etoposide, topotecan), and antibiotics (e.g. bleomycin, doxorubicin) [59]. Kidney excretion (albeit <30%) is reported for small-molecule targeted therapy agents, most of them not requiring dose adjustment in CKD but are often associated with AKI occurrences [60]. Newer immune therapies are represented by larger molecules such as monoclonal antibodies and immune cells, which are not excreted in the urine but are able to impact kidneys through autoimmune responses [61]. The importance of assessing glomerular filtration rate (GFR) to identify patients with KD has been nicely illustrated by data from a nationwide cancer registry, in which 65% of patients with normal serum creatinine had decreased GFR. In this study, roughly 50% of patients had received an inadequate drug dosage [62]. Kidney function assessment in cancer patients is a still an ongoing issue, although Janowitz *et al.* [63] recently validated a body surface area-adjusted CKD Epidemiology Collaboration (CKD-EPI) formula to be used to assess chemotherapy dose. However, current guidelines in oncology still recommend that the standard CKD-EPI formula be applied to cancer patients with KD and Cockcroft-Gault formula in the general population [64], and recent papers in oncology have highlighted this gap between guidelines and reality [65, 66]. Altogether, the implications are that cancer patients should not only be routinely screened for cognitive impairment but should also undergo correct renal function assessment to inform the chemotherapeutic strategy and dosing schedule (Fig. 2).

Parallels between neuroimaging in CRCI and KD

Brain structure abnormalities have been documented in cancer survivors who have undergone chemotherapy [24, 67], including reduced gray matter volume, particularly in the prefrontal cortex, anterior cingulate cortex, and fusiform gyrus, compared with untreated cancer survivors and healthy controls. In addition, individuals who are further along post-treatment exhibit greater volume in the prefrontal cortex [67]. Similarly, gray matter volume reduction in the anterior cingulate cortex is reported for patients with end-stage kidney disease [68] (Fig. 3).

Functional changes also occur after chemotherapy. While completing cognitive tasks, cancer survivors undergoing chemotherapy showed reduced activity of the fronto-parietal attention network in comparison with untreated patients and healthy controls [69]. This may reflect their difficulty in focusing on cognitive tasks, inability to recruit brain resources needed for the task, or may be attributable to chemotherapy-related structural abnormalities in the brain. Studies of resting-state functional connectivity also demonstrate differences between patients who have undergone chemotherapy and untreated controls [70]. There is also experimental evidence of loss of neural precursor cells that form neurons throughout life, as well as interruption of synapses between neurons, contributing further to cognitive decline [71]. Similar

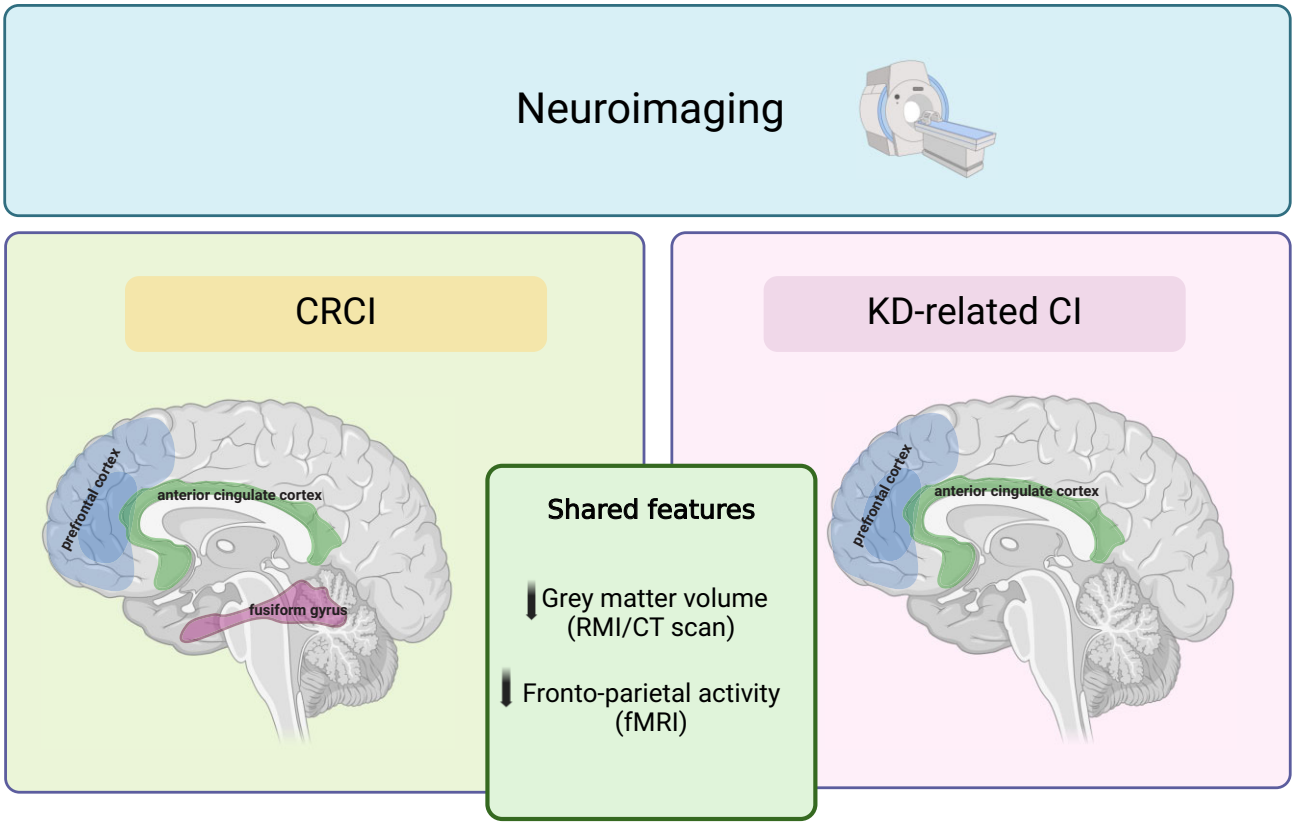

Figure 3: The figure highlights similar structural and functional neuroimaging findings in both CRCI and KD-related CI. Created in BioRender. Hafez, G. (2024) https://BioRender.com/w92g921.

functional patterns were observed in CKD patients [72] studied by fMRI, highlighting once again a significant parallelism between CI in KD and CRCI (Fig. 3).

A sophisticated retrospective machine learning-based analysis of whole-brain functional connectivity (also referred to as connectome) in breast cancer survivors previously treated with chemotherapy revealed that CRCI is not a binary condition and different CRCI biotypes can be identified [73]. In breast cancer patients undergoing chemotherapy, three CRCI biotypes have been identified through a sophisticated integrative analysis based on connectome, an entity including cognitive performance variables, functional and structural brain features studied by fMRI, as well as clinical and demographic factors [73]. These biotypes range from low (biotype 1), to mild (biotype 2), to severe (biotype 3) grade and showed stronger separation of CRCI characteristics compared with more traditional classification of presence or absence of symptoms and could lead to more personalized treatment approaches. For example, Biotype 1 might benefit from treating symptoms of anxiety and fatigue, Biotype 2 may need to address sleep hygiene, and Biotype 3 may respond best to cognitive training or rehabilitation [74]. It would be interesting to include kidney function data in future studies, to determine if there are specific CRCI biotypes affected by kidney function.

Neuroimaging and metabolic studies have demonstrated that chemotherapy can alter cerebral blood flow and glucose metabolism in the brain. Using positron emission tomography, researchers observed decreased glucose metabolism in specific brain regions of breast cancer survivors treated with chemotherapy [24]. Specifically, investigators found reduced glucose metabolism in the left inferior frontal gyrus and the contralateral cerebellum. Significant decreases in basal ganglia metabolism were also observed in patients treated with both chemotherapy and tamoxifen [27]. Early similar evidences were also found in patients with impaired renal function [75].

Regrettably, none of aforementioned imaging studies conducted with cancer patients included kidney function data, which restricts our ability to draw conclusions regarding whether kidney dysfunction exacerbates CRCI-related brain structural and functional alterations. However, it is crucial to emphasize the similarities found in the two conditions in separate studies.

CRCI MANAGEMENT STRATEGIES: SHARED BENEFITS FOR CANCER AND KD PATIENTS

Addressing CRCI requires a multidisciplinary approach and a combination of supportive therapies, especially in the presence of comorbidities such as KD.

Non-pharmacological approaches

Owing to the complexity of CRCI mechanisms, various non-pharmacological approaches have been suggested to alleviate symptoms. Modification of lifestyle, especially exercise, could positively affect brain function. Indeed, physical exercise has been shown to prevent cognitive impairment associated with chemotherapy by enhancing hippocampal neuroplasticity and mitochondrial function [76]. Recent observational studies in cancer patients who received chemotherapy have reported positive associations between cognitive function and aerobic exercise, measured by self-report, accelerometers, and aerobic fitness [77]. A recent systematic review of randomized controlled trials in humans assessed the impact of physical and mind–body exercise on

CRCI. Of the trials identified in this review, 13 (45%) reported a benefit of exercise resulting in improved cognitive function [77]. Similarly, exercise has been shown to improve cognitive functioning related to KD. A cycle of 24 weeks of exercise training allowed a significant improvement of both general and specific cognitive functions (memory, attention, executive, and verbal), even in patients with moderate-severe CKD older than 65 years [78]. Similar evidence has been also reported for hemodialyzed patients [79].

Cognitive training (or sometimes called brain training) is a behavioral intervention utilizing repetitive cognitive exercises to improve cognition. Studies have reported positive outcomes in both cancer [80] and hemodialyzed [81] patients. These exercises offer potential benefits in restoring neural pathways impacted by CRCI and CI in KD [78]. In addition, employing coping strategies tailored to individual needs such as exploring alternative approaches to daily activities can enhance focus and retention. Techniques such as note-taking or structuring information while reading may prove beneficial. Implementing stress-relief methodologies and addressing stressors is crucial [82], as they can exacerbate memory difficulties and *vice versa*. Learning relaxation and mindfulness-based techniques can assist in stress identification and management, breaking the cycle of stress-induced memory impairment [83].

Pharmacological approaches

As mentioned previously, the most important pharmacological approach to prevent CRCI relies on correct dosing of chemotherapeutics and adjustment to renal function is fundamental even in cancer patients with apparently normal creatinine.

Currently, there are no FDA-approved medications specifically for the treatment of CRCI. However, the strategy of repurposing existing drugs, originally developed for other neurological disorders, could potentially be effective. Several pharmacological interventions have been identified that target some of the underlying mechanisms of CRCI (oxidative stress, vascular damage, neuroinflammation, neurotransmitter dysfunction, and decreased neurogenesis). These include erythropoietin for anemia correction [8], antithrombotic drugs to limit vascular damage [84], and different psychostimulants such as methylphenidate, modafinil, memantine, fluoxetine, cysteamine and histone deacetylase inhibitors (such as belinostat, panobinostat, and givinostat) and their associations to increase neuronal activity and plasticity [7]. However, the administration of these drugs, also found useful in KD patients [28], requires dose adjustment to kidney function and does not fully cover the intricate pathophysiology of CRCI. The development of new targeted medications to treat CRCI is heavily reliant on our comprehensive understanding of the molecular pathways in the brain that are affected by chemotherapy, as well as the resulting behavioral responses [85]. To address this issue, it is crucial to conduct rigorous pre-clinical and clinical efficacy studies specifically designed to investigate CRCI, as well as the intersection of CRCI and KD.

CONCLUSION

CRCI affects various cognitive domains and significantly impacts cancer patient and survivor quality of life. Impairments can range from subtle to severe and may be either temporary or permanent. Additionally, the high prevalence of kidney failure in oncologic patients may further negatively impact the cognitive performance by possibly potentiating shared underlying mechanisms. CRCI and KD-related CI share many similarities in clinical presentation and imaging findings reinforce this link. General therapeutic recommendations applicable to CRCI in cancer patients could potentially be extended to those comorbid with KD. Precise dosing of chemotherapeutics in the light of kidney function is crucial and necessary to address in oncology, with dose adjustment to pharmacological interventions based on kidney function recommended.

In conclusion, our review highlights the multifactorial origin of CRCI and the complex interplay between CRCI and KD, a common comorbidity and/or complication in cancer patients. Future studies should explicitly examine the impact KD has on CRCI in this patient population, and further develop treatment strategies or interventions to prevent or reverse such cognitive impairments.

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DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

Carsten Alexander Wagner has received honoraria from Kyowa Kirin and Medice. Other authors declare no conflicts of interest related to this work.

APPENDIX

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