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REVIEW

Chemotherapy-induced cognitive impairment: focus on the intersection of oxidative stress and TNFα

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Abstract

Chemotherapy-induced cognitive impairment (CICI) has been observed in a large fraction of cancer survivors. Although many of the chemotherapeutic drugs do not cross the blood–brain barrier, following treatment, the structure and function of the brain are altered and cognitive dysfunction occurs in a significant number of cancer survivors. The means by which CICI occurs is becoming better understood, but there still remain unsolved questions of the mechanisms involved. The hypotheses to explain CICI are numerous. More than 50% of FDA-approved cancer chemotherapy agents are associated with reactive oxygen species (ROS) that lead to oxidative stress and activate a myriad of pathways as well as inhibit pathways necessary for proper brain function. Oxidative stress triggers the activation of different proteins, one in particular is tumor necrosis factor alpha (TNFα). Following treatment with various chemotherapy agents, this pro-inflammatory cytokine binds to its receptors at the blood–brain barrier and translocates to the parenchyma via receptor-mediated endocytosis. Once in brain, TNFα initiates pathways that may eventually lead to neuronal death and ultimately cognitive impairment. TNFα activation of the c-jun N-terminal kinases (JNK) and Janus kinase-signal transducer and activator of transcription (JAK/STAT) pathways may contribute to both memory decline and loss of higher executive functions reported in patients after chemotherapy treatment. Chemotherapy also affects the brain's antioxidant capacity, allowing for accumulation of ROS. This review expands on these topics to provide insights into the possible mechanisms by which the intersection of oxidative stress and TNFA are involved in chemotherapy-induced cognitive impairment.

Keywords Chemotherapy induced cognitive impairment · Oxidative stress; · Pro-inflammatory cytokines · Neuronal death

Introduction

Chemotherapy

Chemotherapy-induced cognitive impairment (CICI), sometimes referred to by patients as "chemobrain" or "chemofog", was first reported approximately 30 years ago [1]. While cognitive dysfunction might be expected in patients diagnosed with brain-resident tumors, CICI also occurs in patients without primary central nervous system (CNS) tumors [2]. Many patients diagnosed with various types of cancers reported lingering side effects following cessation of their chemotherapy treatments [1]. For example, breast cancer survivors often complained that cognitive impairment is the most troublesome post-treatment symptom, leading to a diminished quality of life characterized by decreased neuropsychological performance with effects mostly in working memory, executive functions, processing speeds, and cognitive processes, i.e., chemobrain or chemofog [3–7]. Chemotherapy has been associated with decreased neurogenesis and decreased cell proliferation along with release of inflammatory cytokines in the periphery [3].

Breast cancer patients were studied: pre-treatment, post-treatment, and 6 months post treatment and were found to have decreased cognitive reserve, increased anxiety, and depression from pre-treatment to 6 months post treatment

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[6]. Cognitive deficits were described in some patients even prior to treatment with further decline after treatment, which can persist even up to 15 years post treatment [1]. Breast cancer patients with either stage 1, 2, or 3 cancer had lower cognitive performance compared to healthy or stage 0 cancer patients [7]. Different chemotherapy treatments may lead to varying levels of CICI [8].

Through the aid of preclinical animal studies, mechanisms for CICI have been proposed [3]. The effects of CICI were studied in cancer-naïve, female Sprague–Dawley rats showing significant decreased novel object recognition (NOR) performance and decreased [^{18}F]-fluorodeoxyglucose (^{18}F-FDG) uptake. This study suggested long-term impairment of the frontal cortex as a plausible contributor to the mechanism of CICI [9]. Mice were treated with doxorubicin (DOX), a chemotherapeutic agent that produces ROS via redox cycling of its quinone structure, leads to decreased cognitive performance assessed by NOR [10]. Another chemotherapy agent, methotrexate, was shown to lead to cognitive deficits through vascular toxicity and elevated peripheral and central TNFα [11]. The effects of 6 cytotoxic agents were tested on C57BL/6 J mice (cyclophosphamide, docetaxel, doxorubicin, 5-fluorouracil, methotrexate, and topotecan). Mice were sacrificed 3 or 15 weeks and the effects on neurogenesis, blood vessel density, and neuroinflammation were studied. No effect was seen on neurogenesis, increased blood vessel density in the hippocampus and prefrontal cortex, but a decrease in the number of microglial cells was observed. The decrease in microglial cells is consistent with inflammation after treatment [12]

An at-first mystifying aspect of CICI is that most chemotherapy agents do not cross the blood–brain barrier (BBB); however, these agents are associated with significant damage to the brain and CNS and can lead to CICI [13]. The number of possible causes of CICI is extensive, as the exact cause has not been definitively determined. Potential causes of CICI, among others, stem from the cancer itself and cancer treatment, altered brain biochemistry, genetic predisposition, possible tumor metastases to the brain, increased permeability of BBB due to decreased structural integrity, and DNA damage [2, 13]. Neuroinflammation is one of the leading hypotheses in the mechanisms underlying mental health problems, depression, and anxiety associated with CICI [14]. Complete surgical resection of a non-metastatic orthotopic, syngeneic mammary tumors in a rat model reversed the tumor-induced increased levels of circulating cytokines [14].

Adult neurogenesis occurs in niche regions within the brain; however, reduced neurogenesis is reported in chemotherapy-treated patients, increasing the risk of cognitive impairment [15]. Neurons are highly polarized and use spines and dendrites to regulate synaptic plasticity, which plays an important role in learning, memory, and executive function. Loss of these spines and dendritic arborization is observed post treatment [15]. This process can lead to decreased neurotransmitter release, inflammation, and the breakdown of the BBB [16].

Chemotherapy often causes changes in brain structure

The effects on the brain due to chemotherapy treatments likely contribute to cognitive impairment [1]. Structural changes and inflammation in the brain following chemotherapy were observed by neuroimaging techniques, such as magnetic resonance imaging (MRI) as well as functional MRI (fMRI) [1]. Reductions in white and gray matter one year after treatment were observed as well as decreased activation in prefrontal cortex and hippocampus [1]. Reduced white matter integrity can be observed 10 months to 10 years post treatment [3]. In a study of cerebral white matter integrity, the chemotherapy group performed worse in attention, psychomotor speed, and memory [17]. White matter is necessary for communication between different brain regions with its integrity important for proper brain function.

Cancer survivors diagnosed with CICI tend to have an inverse correlation with intensity of the effects of CICI and the time after treatment, suggesting recovery from chemobrain [15]. However, in contrast to this suggestion, other studies show diminution of cognition associated with chemotherapy can last at least a decade [15]. Decreased gray matter is seen in several regions immediately following chemotherapy treatments with partial recovery a year later [15]. Consistent with these findings, one month after chemotherapy completion, decreased gray matter is observed in breast cancer patients [18]. This aspect of CICI requires further investigation.

Recent studies suggest that chemotherapy itself can damage brain structure with a connection to cytokine dysregulation that impairs synaptic networks, hippocampal volume, and brain metabolism in the prefrontal and temporal cortex [11]. Chemotherapy-associated release of inflammatory cytokines in the periphery can lead to immune dysregulation. Induction of central inflammatory cytokines can cause activation of microglia [3] (Fig. 1).

Chemotherapy-induced oxidative stress results in the activation of the TNFα cascade

Cytokines and Inflammation

Microglia are considered the immune cells of the CNS and respond to most kinds of pathology [19]. When microglial

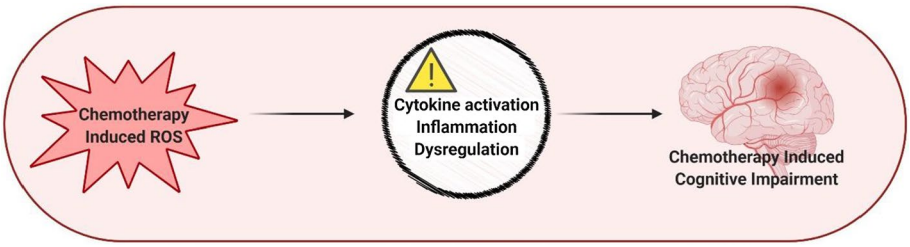

Fig. 1 Summary of cytokine-related mechanism of CICI discussed in this current review

cells are fully activated, they can be neurotoxic, following release of ROS, inducible nitric oxide synthase (iNOS) and TNFα. Cytokines play an important role in cell signaling by regulating immune and inflammatory responses [16]. Under normal conditions, inflammatory response and cytokine release are regulated [20]. Importantly, cytokines reportedly play a role in cancer progression and development [21]. Pro-inflammatory cytokine production has been suggested as a candidate mechanism for cognitive dysfunction [13, 22]. There are multiple conditions and stressors that may contribute to increased production of cytokines, which, among others, include cancer, acute and chronic stressors, physical and psychological stressors, and chemotherapy [21]. However, it is the increased complaints of cognitive dysfunction from patients following chemotherapy treatment that suggest these treatments are correlated to brain dysfunction [16].

Circulating cytokines can reach the brain via several pathways leading to stimulation of microglial cells [20], 23. Communication between the peripheral cytokines and those in the CNS occurs through active transport across the BBB, passive transport through leaky regions of the BBB, receptor–ligand endocytosis, or stimulation through local inflammatory networks [21]. One cytokine, in particular, has been observed to play a major role in CICI: TNFα.

TNFα is a key player in pro-inflammatory cytokine cascades. TNFα is upstream of IL-1 and elicits the latter's production within the brain [24]. IL-1β is pivotal for hippocampal learning in memory, however, high levels interfere with long-term potentiation and synaptic plasticity [24]. In mice following surgery, TNFα is detectable within the first 30 min and is the first cytokine to be released, while others are not detectable until 6 h post-surgery [24]. However, pre-operation administration of anti-TNF antibody reduced systemic IL-1β. Trace fear conditioning also was performed in mice, and post-operation hippocampal-dependent memory impairment was observed. Pretreatment with anti-TNF antibody ameliorated cognitive decline [24].

In addition to in animal studies, plasma TNFα levels have been correlated with cognitive impairment in breast cancer patients. In two groups of patients, before chemotherapy (BCG) and after chemotherapy (ACG), plasma cytokine levels were evaluated (Am J TRANSL RES). The BCGs were further categorized into two groups, cognitive impaired group (CIG) and cognitive normal group (CNG). Higher levels of IL-1β, TNFα, and IL-4 were seen in ACG compared to BCG. The CIG also showed higher levels of the three cytokines compared to the CNG [25]. Two correlations were seen in the BCG, a direct correlation between cognition and quality of life and an inverse correlation between cognitive function and cytokine levels [25].

Post-chemotherapy patients reportedly demonstrated an increase in the soluble TNF receptor II (sTNF-RII). Higher baselines for the receptor were seen in patients with memory complaints, consistent with the notion that a post-chemotherapy increase in TNFα may play a role in the decline of cognition [26]. Blood cytokine levels of early-stage breast cancer patients were measured pre-surgery, post-surgery (prior to chemotherapy), and 6 months post-chemotherapy. At 6 months, the women reported a decline in quality of life and an increase in fatigue. An increase in sTNFRII, interleukin-6, and interleukin-10 was observed only in the post-chemotherapy group [27]. An increase in TNFRI and TNFRII is correlated to an increase in TNFα. The majority of biological effects of TNFα are mediated through its interaction with TNFRI [28]. Interleukin-10 is essential for exercise-induced analgesia; however, interleukin-10 has been suggested to resolve neuropathic pain induced by chemotherapeutics such as cisplatin [29]. Complete surgical resection of a non-metastatic orthotopic, syngeneic mammary tumor reversed the tumor-induced increases of circulating cytokines [14].

Activation of TNFα via ROS

Different chemotherapeutics induce damage to cancer cells via varying mechanisms. Alkylating agents such as cyclophosphamide cause DNA damage, antimetabolites, methotrexate and 5FU, disturb function and biosynthesis of DNA or RNA leading to cell death, and anti-microtubule agents, paclitaxel and docetaxel, interfere with cell division and proliferation [3]. In this review, we will focus on doxorubicin (DOX) for its cytotoxic effects through the production of ROS. DOX, used for the treatment of solid tumors and lymphoma, generates intracellular ROS evidenced by the observation that the intraperitoneal administration of DOX generates an increase in TNFα and oxidative damage in plasma and brain in mice [30]. The quinone structure

in DOX undergoes redox cycling between the quinone and semi-quinone radical, producing superoxide free radical in the presence of oxygen [31]. Patients treated with DOX had an increase in plasma oxidative stress and protein carbonylation as well as an increase in TNFα 6 h after treatment [30].

DOX has been shown to damage plasma proteins and increase TNFα levels in the periphery and in the brain [30, 31]. To gain insights into these observations, J774A.1 macrophage cultures were incubated with potassium superoxide, KO_2, which when dissolved in aqueous solution releases superoxide radicals; increased TNFα levels were observed, consistent with the notion that the superoxide free radical produced from DOX under redox cycling is connected to the increase in TNFα [32]. Lipid peroxidation in brain from mice occurs after injection intraperitoneally with DOX [33]. Although DOX does not cross the BBB, this chemotherapeutic agent induces a strong TNFα immunoreactivity in the cortex and hippocampus of DOX-treated mice. In addition, DOX increases pro-apoptotic factors, such as p53 and Bax, in brain mitochondria and increased release of cytochrome c and caspase-3 was noted following DOX treatment, consistent with apoptotic brain cell death [34].

To solidify this concept that TNFα is involved with oxidative damage in brain following treatment with BBB-impermeable DOX, mice with the gene for TNFα knocked out were investigated. TNF knockout mice had significant amelioration of oxidative stress in the brain as well as preservation of brain mitochondria function following DOX treatment [35]. In plasma, apolipoprotein A1 (ApoA1) inhibits the production of TNFα, however ROS in plasma causes oxidation of ApoA1 and promotes TNFα to interact with receptors on the BBB that lead to endocytic transfer to brain parenchyma [16]. DOX also activates microglia and astrocytes through TNF receptor 1 (TNFR1), which triggers iNOS release and therefore an increase in ROS and reactive nitrogen species (RNS) [36]. Supportive of the role of TNFA in CICI in the studies noted above, rats treated for four weeks with interferon-β-1a or Infliximab, both TNFα inhibitors, protected against DOX-induced chemo-brain [37].

Induction of the JAK-STAT pathway amplifies the signal from TNFα

Signal transducer and activator of transcription (STAT) mediates a vast array of processes that are required for homeostasis and development [38]. STAT activation induces cytokines and growth factors. Janus kinases (JAKs) phosphorylate and activate STAT monomers in the cytoplasm leading to homo- or heterodimerization [38]. JAK-STAT pathways relay signals from cellular membrane receptors to the nucleus and are involved in the pathways of cytokines, as the JAK-STAT enzymes are bound to the cytoplasmic regions of cytokine receptors [39]. Oxidative stress activates these pathways evidenced by STAT1 and STAT3 activation in response to H_2O_2 [40].

TNFα and IL-6 were elevated in bone marrow aspirates of multiple myeloma patients, and the JAK-STAT pathway was directly involved in TNFα signaling pathways [41]. In murine samples, TNFA induced tyrosine phosphorylation and activation of JAKs, which was associated with tyrosine phosphorylation of STAT [42]. Activation of JAK-STAT pathways via TNFα leads to other cytokine activation. The majority of immune responses initiated by cytokines are dependent on STAT activation [38]. JAK-STAT induction of cytokine production along with TNFα initiation of other cytokines can lead to an amplification of effects of pro-inflammatory cytokines.

Activation of MAPK pathways follow TNFα activation of the JAK-STAT pathway

Mitogen-activated protein kinases (MAPK) are important signaling molecules and are classified in four groups: (1) extracellular signal-related kinases (ERK), (2) c-jun N-terminal (JNK) or stress-activated protein kinases (JNK/SAPK), (3) ERK5/big MAP kinase 1 (BMK1), and (4) the group of p38 MAPKs [43]. JNKs respond to cellular stresses, ERKs are important for signal transduction, and the p38 MAPK group is involved in inflammation, cellular growth, cell cycle, and cell death [43]. There are three isoforms of JNKs with JNK3 being expressed primarily in neuronal and cardiac cells [44]. These enzymes phosphorylate and regulate activity of transcription factors and are activated by MAPK modules. JNKs are pro-apoptotic kinases that play a role in apoptosis of neurons, especially TNFα-induced apoptosis as JNK is a downstream protein of the TNFα pathway [44]. The group of p38 MAPKs is activated by environmental stressors, growth factors, and MAP kinase kinase kinase (MAP3K) plays a role in the activation of both JNK and p38. Inflammation is a major activator of p38, which then plays a role in the production of cytokines, such as interleukin-1β, interleukin-6, and TNFα [43]. ERKs are phosphorylated in response to mitogens and are involved in signaling for cell proliferation [45].

When DOX and cisplatin were administered together, activation of the JNK/p38 MAPK pathway and an increase in cytochrome c release from mitochondria were observed [46]. This observation is consistent with the notion that enhanced activation of JNK/p38 may lead to mitochondrial intrinsic apoptotic pathways [46]. As noted above, pro-inflammatory cytokines enter the BBB through receptor-mediated transport inducing the JNK/p38 MAPK pathway, which has been shown to be triggered by DOX [16]. Carmustine, an alkylating chemotherapeutic agent used to treat brain tumors, caused an accumulation of ROS via glutathione reductase

inhibition triggering a concentration- and time-dependent cell death of neuronally differentiated cells in association with increased caspase-3 activation and induction of phosphorylation of MAPKs, such as ERK, JNK, and p38. Inhibitors of these proteins prevented cell death via carmustine suggesting carmustine may induce cell death through these pathways [47].

DOX treatment led to increased mitochondrial apoptosis pathways evidenced by increased Bax to Bcl-2 ratios. MAPKs, ERK and p38 expressions also were altered after DOX administration [36]. Rats dosed with DOX led to increased pERK and p-p38 MAPK in sensory neurons and cortical neurons, blocking long-term synaptic facilitation (LTF). LTF was rescued in the presence of a p38 MAPK inhibitor, suggesting long-term memory impairment via the p38 MAPK pathway [48]. Ovariectomized rodents were given a drug cocktail of cyclophosphamide and DOX (AC-chemo), and the levels of pro-inflammatory cytokines and oxidative stress response gene markers were evaluated. ERK1/2 and JNK/SAPK signaling activities were elevated in the hippocampus [49] (Fig. 2).

Neuronal death in chemobrain is seen in a decrease in BDNF

Brain-derived neurotrophic factor (BDNF) plays a role in the survival and differentiation of neurons [50]. New neurons involved in memory and learning require BDNF to nurture the processes of adult neurogenesis. 5-fluorouracil (5-FU) disrupts cell proliferation and readily crosses the BBB. The effect of 5-FU on spatial working memory in mice was determined. 5-FU significantly reduced hippocampal BDNF and doublecortin protein levels associated with marginal disruption in spatial working memory. Reduced levels of BDNF and doublecortin in the hippocampus are indicative of alterations in neurotrophin levels and neurogenesis [51].

Exercise, which is reported to elevate brain levels of BDNF [52], has been known to positively affect brain function. Wistar rats, separated into four groups: control, control + exercise, chemobrain, and chemobrain + exercise were studied. Cognitive dysfunction was induced by DOX administration for four weeks. Exercise was completed via low-intensity treadmill for 6 days a week for the four weeks. The chemobrain group showed a decline in cognitive function, neurogenesis, and BDNF in the hippocampus. However, exercise attenuated these impairments in cognitive function and neuroplasticity for those with chemobrain [53].

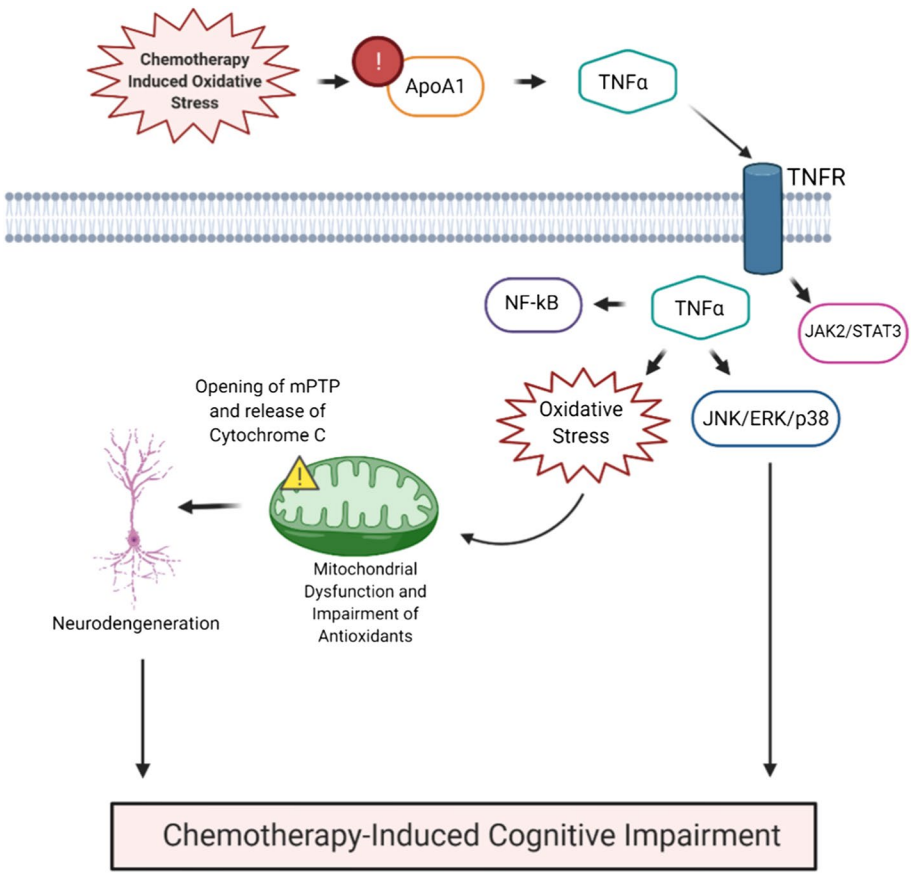

Fig. 2 Anti-cancer treatments trigger ROS production and oxidative stress in the periphery inducing an increase in TNFα. TNFα interacts with its receptors in the bilayer activating the JAK/STAT pathway. Increased TNFα within the cytoplasm results in oxidative stress and impairment of antioxidants. Mitochondrial dysfunction leads to mPTP opening and Cyt. C release followed by neurodegeneration and CICI. JNK/ERK/p38 activation through TNFα also results in CICI.

Chemotherapy reduces ability for cellular defenses to combat effects of cognitive impairment

Although most chemotherapies do not cross the BBB, with some exceptions, they have been associated with cell death and decreased cell division as well as decreased antioxidant capabilities [13]. Glutathione (GSH), a major intracellular antioxidant found ubiquitously in the brain, under the action of glutathione peroxidase (GPx), scavenges H_2O_2, which is converted to H_2O and O_2 via oxidation of GSH to glutathione disulfide (GSSG) [35]. GSSG is then converted back to GSH via glutathione reductase (GR). In DOX-treated mice, however, an increase in peripheral TNFα was observed [34, 35]. Decreased GSH levels in brain also were observed as well as decreased GSH/GSSG ratios [35], a marker of elevated oxidative stress upon Dox treatment. An increase in GSSG or a lack of activity of GR means that the powerful oxidative stress protection of GSH is lost after DOX treatment, which can result in oxidative stress-mediated neuronal dysfunction. Other antioxidants are also seen to be altered in brain after chemotherapy treatment. After intraperitoneal treatment of mice with DOX, a reduction in activity of the antioxidant enzyme manganese superoxide dismutase (MnSOD) in brain was observed, likely resulting from nitration of key Tyr residues in this protein and leading to more oxidative and nitrosative stress [54]. This is because MnSOD is a highly efficient enzyme for scavenging superoxide free radicals, particularly since this enzyme is mitochondrially resident, and mitochondria are a large source of superoxide free radical due to inefficiency of Complex I [31, 61].

Co-administration of protective agents with DOX may help to ameliorate the effects of DOX on the brain. For example, astaxanthin, a carotenoid antioxidant, anti-inflammatory and anti-apoptotic agent, reportedly protects against DOX-induced memory impairment. Administration of astaxanthin was able to restore hippocampal histopathological architecture and halted DOX-induced oxidative damage [55]. All three astaxanthin isomers were shown to reduce TNFα-induced secretion of interleukin 8 by 22–27% by inhibiting TNF-induced Nf-kB activation [56]. Another antioxidant, N-acetyl-cysteine (NAC) raises brain levels of GSH [57]. NAC is an approved FDA drug which provides the necessary cysteine, which is the rate-limiting substrate for the synthesis of GSH. NAC itself can act as an antioxidant scavenging for ROS as well as raise cysteine levels for GSH production [57]. In clinical studies, 40 children newly diagnosed with acute lymphoblastic leukemia were evaluated for the effects of NAC coupled with vitamin E. Twenty children took the combination vitamin E and NAC supplements, while the other 20 took a placebo. Glutathione peroxidase, malondialdehyde and TNFα levels were measured. Compared to the placebo group, a reduction in chemotherapy- and radiotherapy-mediated toxicity was observed as indicated by an increase in glutathione peroxidase levels [58].

Sodium-2-mercapthoethane sulfonate (MESNA), due to its negative charge does not enter cancer cells and therefore does not interfere with cancer chemotherapy [59]. The -SH moiety on MESNA efficiently binds the lipid peroxidation product, HNE, preventing its toxic effects [20]. Treatment of mice with MESNA significantly modulated oxidative stress in brain and prevented cognitive loss assessed by NOR [8]. MESNA was shown to have poor cellular uptake by most cell types allowing it to act as an antioxidant in urine and blood and not interfere with the effects of the chemotherapeutic drug [59]. Co-administration of MESNA with DOX reduced post-treatment levels of TNF-related cytokines and TNFR1/2 [59]. Patients not treated with MESNA showed a statistically significant increase in proteins adducted by 4-hydroxynonenal (HNE) compared to those treated with MESNA [30]. Mulmina, a formulation of natural compounds known to help improve function and prevent cognitive decline, was given to normal rats also injected with a combination of cyclophosphamide, methotrexate, and 5-FU (CMF). Those injected with mulmina showed significant improvements in cognitive function post chemotherapy [60].

Antioxidant therapy for cancer patients has to be carefully considered. For example, elevation of brain levels of GSH by i.p. injection in mice of γ-glutamylcysteine ethyl ester (GCEE) led to protection against elevated oxidative stress associated with DOX treatment, indicating that free radicals are involved in brain effects induced by DOX-induced, TNFA-mediated oxidative damage in brain [33]. However, cancer cell-permeable antioxidants have the risk of lowering the redox state of cancer cells and allowing GSH-mediated, glutathione-S-transferase-facilitated binding to chemotherapeutic agents. Such GSH-chemotherapy agent complexes are excellent substrates for the multi-drug resistance protein-1 (MRP-1), which effluxes these complexes out of the cancer cell. That is, the therapeutic efficacy of chemotherapy agents is potentially drastically reduced with such agents [33]. In contrast, MESNA mentioned above, does not enter cancer cells and thereby eliminates these concerns. Moreover, selected redox-sensitive antioxidants have the property of raising the already higher redox state of cancer cells to an even higher state, exceeding the apoptosis threshold, leading to cancer cell death without affecting non-cancer cells appreciably [61].

Conclusion

CICI is often observed in cancer patients without CNS tumors, but the underlying mechanisms by which this quality-of-life diminution is caused have not been definitively

elucidated. Numerous hypotheses have been formed for the cause to CICI, with one being the production of ROS from chemotherapy treatments leading to the activation of pro-inflammatory cytokines such as TNFα that cross the BBB and lead to neuronal death. Although many patients seem to recover slowly over time after chemotherapy treatments end, understanding the mechanisms by which CICI occurs and how to combat this impairment will allow for better quality of life outcomes for the ever-growing number of cancer survivors as a result of improvements in cancer treatment.

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Declarations

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