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REVIEW ARTICLE

Chemotherapy and cognition: comprehensive review on doxorubicin-induced chemobrain

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Abstract

Chemobrain refers to a common sequela experienced by a substantial subset of cancer patients exposed to chemotherapeutic treatment, a phenomenon that dramatically deteriorates the survivors' quality of life and prevents them from restoring their pre-cancer life. This review is intended to address the current knowledge regarding the mechanisms underlying the pathophysiology of the chemobrain phenomenon, with special focus on the antineoplastic agent ''doxorubicin'', which has been shown to be implicated in strenuous central neurotoxicity despite being—almost entirely—peripherally confined. Moreover, the assessment of the post-chemotherapy cognitive impairment in both human and animal subjects, and the potential pharmacotherapy and behavioral intervention strategies are reviewed.

Keywords Chemobrain · Doxorubicin · Hippocampus · Memory · Neuropsychological tests

Introduction

Chemotherapy has been proven to be a cardinal cornerstone in cancer management [1]; however, patients receiving chemotherapeutic agents are often plagued with numerous debilitating side effects [2]. Chemobrain (also known as post-chemotherapy-induced cognitive dysfunction) was first reported in 1980 when patients with diverse types of malignancies scored significantly lower in tests assessing cognitive functions during and after chemotherapy administration [3]. Chemobrain imputes memory impairment, slow processing speed, inability to concentrate, and language difficulty. It is classified by the National Cancer Institute as one of the most debilitating sequelae of cancer therapy, which precludes patients from resuming their pre-cancer life [4]. Regarding its prevalence/incidence, chemobrain or chemotherapy-related cognitive impairment (CRCI) is estimated to occur in 17–75% of patients receiving cancer chemotherapy [5]. Furthermore, Schagen and Wefel [6] revealed that the incidence of chemobrain is still a research subject and about 17–78% of patients would be affected. In addition, 17–30% of the affected patients appear to sustain long-term cognitive impairment after chemotherapy [7]. Breast cancer patients receiving adjuvant chemotherapy were found to be one of the most documented classes of patients suffering from incessant deterioration in cognitive functions (decline in learning new information and accelerated forgetting new information, decline in executive function and psychomotor speed) [8].

Chemobrain differs from other neurodegenerative conditions in cues, as they are helpful in chemobrain, whereas in others memory does not respond to cues. In addition, other types of neurodegeneration usually involve personality changes, motor changes (stiffness, tremors, falls) or hallucinations, which are not typical of chemobrain. However, it can be hard to differentiate between age-related forgetfulness and chemobrain where symptoms are mild [9, 10]. Substantially, doxorubicin (DOX) is one of the most frequently administered chemotherapeutic agents to breast cancer patients [11].

DOX is a prominent mainstay member of the anthracycline antineoplastic agents; it is one of the most potent FDA-approved agents for treatment of diverse types of tumors [12]. As shown in Fig. 1, DOX exerts its cytotoxic effect through a set of mechanisms including DNA intercalation and topoisomerase II inhibition causing DNA strand breaks. In addition, DOX undergoes redox cycling leading to the production of large amounts of reactive oxygen species (ROS). Indeed, any of the preceding paradigms ends up in cell death [13]. As expected, the extreme clinical effectiveness of DOX comes at a cost; DOX incites multi-organ

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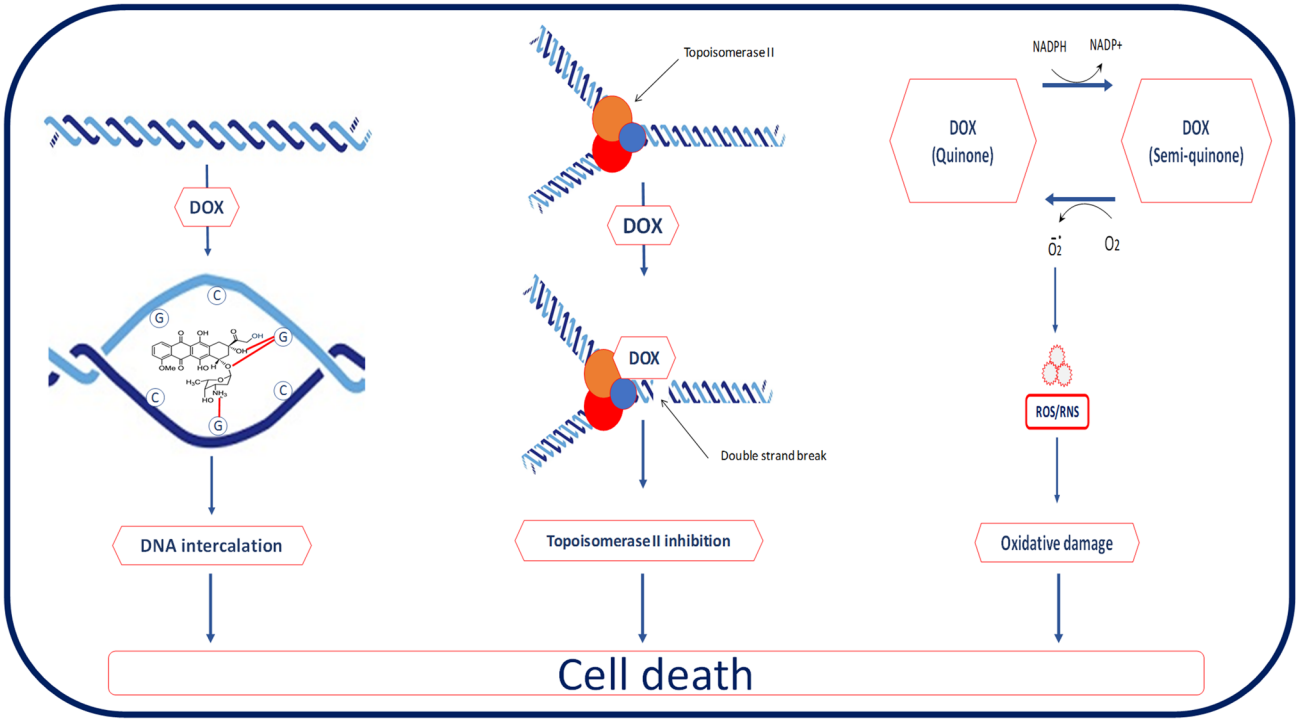

Fig. 1 Mechanisms underlying DOX antineoplastic activity. As a DNA intercalator, DOX prefers the intercalation site containing adjacent guanine–cytosine base pairs. Formation of DOX-DNA adducts has been shown to activate DNA damage responses and induce cell death. DOX also acts by binding to the interface between the introduced DNA breaks and the active site of the topoisomerase II enzyme forming a DOX-enzyme–DNA complex eventually leading to hampering of DNA resealing. Moreover, DOX undergoes redox cycling process leading to production of massive amounts of ROS thus damaging vital biomolecules. Indeed, any of the previous mechanisms end up by cell death

toxicities in the form of a dose-limiting fatal cardiotoxicity, nephrotoxicity, hepatotoxicity, hematopoietic toxicity and central neurotoxicity perceived as a decline in cognitive functions [11, 12].

Memory impairment resulting from chemotherapeutic agents that are directed toward the central nervous system is a well-known phenomenon and regarded as an acceptable compromise of using these agents; however, the ability of antineoplastic agents that are not directed toward the CNS and do not even cross the BBB to adversely affect cognitive functions was a surprising fact. Multiple reports showed that only an inconsiderable amount of DOX crosses the BBB, which is utterly insufficient to elicit antitumor effect [14, 15]. So, the fact that DOX adversely impacts cognitive functions, although it is almost completely incapable of crossing the BBB implies that crossing the BBB is dispensable and hints at an indirect pathway through which DOX incites central neurotoxicity [11]. Some strategies aim to facilitate chemotherapies' crossing of BBB to treat intracerebral tumors such as nanoparticles drug delivery which improves penetration of drugs and their accumulation inside cancer cell to enhance efficacy and reduce toxicity or side effects [16]. In this regard, increasing the rate of drug delivery is termed "dose dense" [17]. For instance, DOX is used in pegylated liposomal form to enhance its efficacy and reduce its toxicity [18, 19]. "Dose dense" chemotherapy may be associated with more chemobrain symptoms; however chemotherapy can cause symptoms regardless of whether that specific drug crosses the blood–brain barrier or not [17].

Taking into consideration the fact that a deep understanding of the pathophysiology underlying chemobrain is indispensable for optimizing clinical outcome and patient's quality of life, in this review article we will summarize and discuss the potential possible mechanisms underlying DOX-induced cognitive impairment.

Mechanisms of doxorubicin-induced cognitive dysfunction

The greatest gap in our knowledge regarding post-chemotherapy-induced cognitive dysfunction is a lack of understanding of the mechanism(s) underlying the observed changes. Herein below, we discuss the potential possible mechanisms underlying DOX-induced cognitive impairment (Fig. 2).

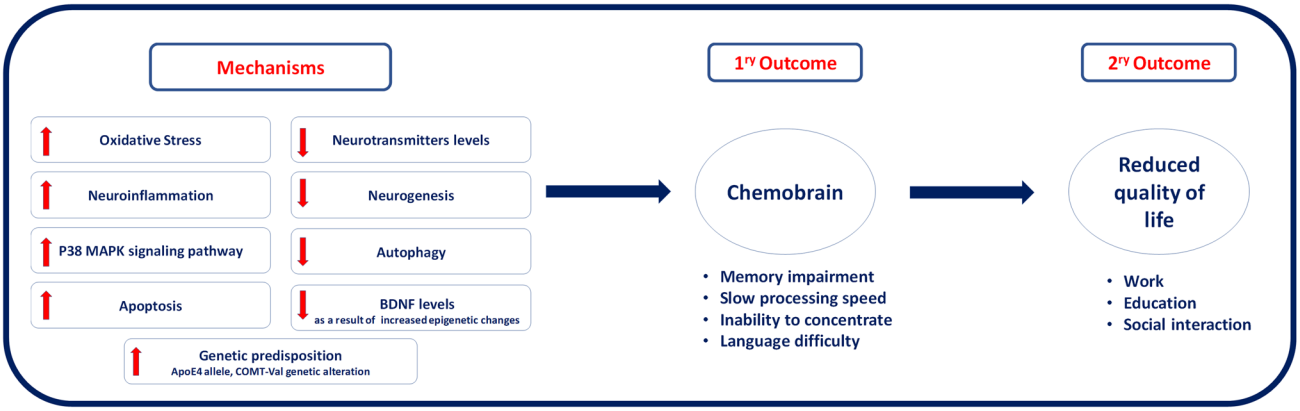

Fig. 2 Summarized mechanistic insight into a multifactorial model of DOX-induced cognitive dysfunction

Oxidative stress

In addition to its role in mediating its anticancer activity, oxidative stress has been reported to be a key-player mediating DOX-induced cognitive deficits [20]. DOX's structure has a quinone moiety that undergoes redox cycling transformation, in which the quinone moiety accepts a single electron and transforms into an unstable semi-quinone intermediate that is converted back to the parent quinone chaperoned with massive amounts of ROS, thus disrupting several fundamental biomolecules. DOX-mediated neurotoxicity is possibly resultant from amplified protein oxidation, lipid peroxidation, decreased glutathione (GSH) level and alteration in antioxidant enzyme levels', including reduction of one of the most crucial mitochondrial antioxidant enzymes, manganese superoxide dismutase (MnSOD) [21, 22]. Tangpong et al. [23] proved that nitration of MnSOD enzymes results in decrease in enzyme activity and consequently decline in mitochondrial respiration. Moreover, the emitted ROS further reacts with nitric oxide producing peroxynitrite, one of the most detrimental RNS, which nitrates tyrosine residues in proteins, hence hampering post-translational modifications of proteins and consequently dynamic signaling pathways [23, 24].

Inflammation

Notwithstanding the key role of ROS in mediating DOX neurotoxicity, the aforementioned mechanism is veracious for introducing ROS into whole body organs except for the brain because DOX is almost completely incapable of crossing the BBB [14]. Therefore, this indicates the existence of an indirect mechanism that does not requisitely involve redox cycling within the CNS. In this regard, it has been reported that ROS generated from redox cycling process activates nuclear factor kappa B (NF-κB), and thus stimulates the transcription of multiple target genes including inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) [25]. Hayslip et al. [4] reported substantial increment in the plasma levels of TNF-α in cancer patients 6 h post-DOX administration among multiagent chemotherapy regimens. Furthermore, Tangpong et al. [23] and Butterfield [26] revealed that treatment with DOX leads to increase in plasma and brain level of TNF-α in wild-type mice and in mice deficient in the inducible form of nitric oxide (iNOSKO).

Moreover, the inflammatory insult could be secondary to DOX-induced apolipoprotein A1 (Apo-AI) oxidative modification [27]. Apo-AI mediates manifold roles in normal body functioning comprising regulation of inflammatory response through depressing the production of inflammatory cytokines, primarily TNF-α, via upregulating the production of a mRNA-destabilizing protein named tristetraprolin which prompts the disintegration of TNF-α mRNA and consequently constrains TNF-α translation [28]. In addition, Aluise et al. [29] and Butterfield [26], proved that oxidized APOA1 enhances or improves TNF-α release or production from macrophages resulting in CNS-toxicity through TNF-α'-mediated oxidative stress in the brain. Hence, Apo-AI oxidative modification leads to a vast production of inflammatory mediators proficient in crossing the BBB. Of the pro-inflammatory mediators released, TNF-α is particularly responsible for perturbing the integrity of the BBB, leading to an incessant feedback loop of inflammation between the periphery and the CNS [30]. TNF-α was also reported to inhibit long-term potentiation in the hippocampal CA1 and the dentate gyrus [31]. Furthermore, strong TNF-α immunoreactivity was reported in the hippocampus of DOX-treated mice [15]. Taken together, inflammation appears to be a pervasive hallmark, with cytokines being the main culprit underlying DOX-induced cognitive deficits [11]. Importantly, substantial evidence correlates the persistent feedback loop of inflammation between the periphery and the CNS to astrocytes.

Astrocytes are a ubiquitous form of neuroglial cells that mediates normal CNS functioning including, but not limited to, regulation of synaptic transmission, neurovascular coupling, and cerebral microcirculation, along with forming and conserving the integrity of the BBB [32–34]. Evidence suggests that astrocytes are a cornerstone in neuroinflammation. Reactive astrogliosis, a response of astrocytic cells to chronic neuroinflammation, inverts the beneficial astrocytic activity into detrimental, with surplus release of inflammatory mediators. This causes a malicious interminable loop of inflammation that subsequently endorses oxidative and nitrosative damage to neuronal cells and reduces neuroplasticity [35].

Neurotransmitters levels

Taking into consideration the fact that cholinergic neurons play an imperative role in hippocampal-dependent learning and memory and critical loss of central nervous system', acetyl choline has been linked to the pathogenesis of various dementia-associated disorders [36]. Pal et al. [37] reported a significant dose-dependent upregulation in the activity of acetylcholinesterase (AChE) in DOX-treated rats, a finding that was further confirmed by our previous work [38]. Furthermore, DOX treatment significantly reduced the level of two monoamines closely correlated with cognitive functions: serotonin (5-HT) and dopamine (DA) [39]. Serotonergic neurons projecting from the median raphe play a fundamental role in regulating hippocampal synaptic plasticity, through an inhibitory control interceded by 5-HT1A receptors. Serotonin depletion was shown to negatively impact hippocampal-dependent declarative memory as evidenced by poor performance in the novel object recognition task [40]. Dopaminergic activity is also crucial for hippocampal cognitive functions. It mediates persistent, long-term memory of hippocampal-mediated acquisition of new paired associates through the activation of D_1/D_5 receptors in the hippocampal area during the time of encoding [41]. Furthermore, Keeneyet al. [27] proved that DOX administration causes significant reduction in choline-containing compounds. It also revealed that DOX causes severe decline in the activity of both phosphatidylcholine-specific phospholipase C (PC-PLC) and phospholipase D enzymes [27].

Neurogenesis

Since the hippocampus is one of the most crucial structures deeply implicated in memory formation and spatial processing, adult-born neuron integration into the circuitry is a pivotal role of hippocampal neurogenesis and, hence, proper maintenance of cognitive functions [42–44]. Although DOX is peripherally confined, treated animals showed a significant decline in neurogenesis as evidenced by significant reduction in the number of cells expressing neuron-specific nuclear antigen bromodeoxyuridine (BrdUrd)-labeled cells [45]. Kitamura et al. [46, 47] also showed that DOX, in combination with cyclophosphamide, reduced cell survival in the dentate gyrus and subgranular zones in rats. Emerging evidence corroborates that the activation of astrocytic cells and the subsequent release of inflammatory mediators is the main perpetrator behind creating an environment that does not sustain neuronal survival [48].

Importantly, TNF-α was reported to possess anti-neurogenic properties evidenced by the reduction in BrdUrd-positive cells in the subgranular zone following its injection [49]. In addition, mice lacking TNF-α receptor-1 (TNFR1) showed increased proliferation in the subgranular zone; therefore, the anti-neurogenic effects of TNF-α are clearly mediated by TNFR1 [50]. Neuroinflammation does not only affect hippocampal proliferation, differentiation and survival, but may also prevent the incorporation of new neurons into the preexisting network as shown by Belarbi et al. [51], who observed that chronic inflammation negatively impacted the recruitment of adult-born neurons into hippocampal network encoding contextual information.

p38 MAPK signaling pathway

Another possible mechanism for DOX-induced cognitive impairment could be its ability to affect key kinase systems involved in memory. As mentioned before, although DOX penetrates the BBB at levels that are totally insufficient for anti-tumor activity, the inconsiderable amount that penetrates is capable of altering synaptic plasticity together with modulating other molecules implicated in memory formation [52, 53]. In *Aplysia* sensory neurons, single DOX treatment inhibited long-term synaptic facilitation (LTF) induced by application of serotonin together with facilitating long-term synaptic depression (LTD) mediated by the neuropeptide Phe-Met-Arg-Phe-NH_2 (FMRFa) application, demonstrating that DOX possibly blocks learning-associated hippocampal excitability changes. DOX also leads to the activation of both extracellular signal-regulated kinase (ERK) and p38 MAPK which exert opposing actions; the former promotes synaptic facilitation, while the latter mediates synaptic depression. However, p38-mediated inhibition of LTF predominates over ERK effects. Moreover, DOX improved the phosphorylation of the downstream transcriptional repressor cAMP response element-binding protein 2 (CREB2), which promotes LTD. These findings provide an additional hypothesis to explain long-term cognitive deficits experienced by patients exposed to DOX [52, 54, 55].

Apoptosis

Activation of apoptotic signaling pathways could considered as an important contributor to chemotherapy-induced cognitive impairment. In this regard, it has been reported that DOX increases mitochondrial susceptibility to calcium-mediated pore opening, leading to mitochondrial swelling, membrane degradation and apoptotic protein release, thus predisposing to neuronal degeneration [15, 56, 57]. The mitochondrial abnormalities was previously rationalized by Tangpong et al. [15], who confirmed the evading role of TNF-α neutralizing antibodies in brain mitochondrial injury which stressed its role in DOX-induced chemobrain. This important remark was previously described by Usta et al. [58] where TNF-α inhibitor "pentoxifylline" voided DOX nephrotoxicity.

Autophagy

Autophagy mediates a protective role in neuronal cells and its dysregulation has been implicated in several neurodegenerative disorders. Moruno-Manchon et al. [59] reported that treatment with DOX impaired the autophagy–lysosome system in cultivated neurons leading to accumulation of autophagosomes and damaged mitochondria. Moreover, significant buildup of lipofuscin, a hallmark of neuronal senescence which indicates a previous exposure to severe oxidative damage, was found in the brain of mice treated with liposomal formulation of DOX [59]. More recent evidence further demonstrated downregulation of pexophagy, the selective autophagy of peroxisomes, leading to the accumulation of peroxisomes and consequent overproduction of ROS. The aforementioned findings accentuate that although DOX poorly crosses the BBB, the negligible amount that permeates could be sufficient to induce a neurotoxic injury [60].

Genetic factors

The subsistence of genetic factors underlying chemotherapy-induced cognitive decline may even pave the way for predicting those at increased risk for cognitive impairments. So far, studies have examined the association between apolipoprotein E (APOE) and catecholamine methyl transferase (COMT) genotypes [61, 62]. APOE glycolipoprotein plays substantial role in neuronal repair following an insult, with the E4 allele specifically linked to disorders characterized by cognitive dysfunction including Alzheimer's, poor cognitive outcomes in stroke and traumatic brain injury, and memory complaints even in normal subjects [63, 64]. The effect of APOE4 was assessed in breast and lymphoma cancer survivors. Those having even one E4 allele scored significantly lower in visual and spatial memory domains along with impaired executive functioning [61].

COMT is involved in the inactivation of the neurotransmitter DA. Apart from DA's prominent role in movement disorders such as Parkinson's disease, it plays a substantial role in learning and memory. Single nucleotide polymorphism in the COMT gene, manifested as substitution of a valine for a methionine at the 158 position, gives rise to an enzyme with significantly higher activity, and hence substantial increment in DA metabolism and potentially predisposes to chemotherapy-mediated cognitive impairment. A cross-sectional study of cancer survivors exposed to chemotherapeutic agents during their treatment reported that survivors possessing the COMT-Val genetic alteration performed poorly on different domains, including attention, motor speed and verbal fluency. Moreover, cancer survivors carrying the COMT-Val modification performed poorly in attention tests than healthy subjects carrying the same genetic modification [62].

Epigenetic (or microRNAome) changes

One intriguing fact is that despite the extreme heterogeneity of chemotherapeutic agents, the consequent cognitive dysfunction is somehow stereotypical. Over and above, although almost all reports unanimously demonstrated a causal link between peripheral cytokines and chemobrain, the question of how "short-lived" cytokines induce a "chronic" impairment prevails. One possible explanation is that chemotherapy induces epigenetic reprogramming and thus eventually leads to persistent impairment [65]. Tumor-bearing mice exposed to chemotherapeutics showed a more pronounced disruption of the post-transcriptional regulation of gene expression, mainly miRNA changes in the prefrontal cortex. miRNA dysregulation was associated with altered levels of brain-derived neurotrophic factor (BDNF), which plays a key role in cognition and memory [66].

Based on our previous work and the highlighted studies in this comprehensive review, the most important mechanism involved in Dox-induced neurotoxicity is estimated to be the inflammatory insult following Dox administration. The pro-inflammatory cytokine (TNF-α) is elevated in plasma and brain, after which, neurotoxicity develops through oxidative stress (ROS and RNS) and apoptosis-mediated signaling.

Impact of chemobrain on subjects' life

According to survivors, chemobrain can be intricate, with many asserting that it is one of the most troublesome morbidities following chemotherapeutic treatment. Survivors

reported diminished quality of life and daily functioning [67]. Several predisposing factors have been identified that may increase the risk of chemobrain such as gender (women may be more at risk than men), age (advancing age "60 ± 5"), education, ánd IQ [6]. Furthermore, dietary factors (vitamin D deficiency), genetic factors and immune response (depression, anxiety, stress, anemia, hormonal levels, cytokines release, pain and fatigue) were also identified [68–70]. In addition, comorbidities and the chemotherapeutic agent itself (dose, duration, administration and adjuvant or synergetic therapy) were also discussed [71–73].

Many breast cancer survivors complained of slower processing speed and difficulties in multi-tasking which become more evident once they try to resume their work especially for those in intellectually demanding jobs. Wagner et al. [74] reported that 63% of survivors conveyed concentration and attention difficulties, 50% reported memory problems and 38% acquainted problems with abstract reasoning. The current literature accentuates that chemobrain is real, persistent and with subversive impact on quality of life demonstrated as constant daily struggles [75].

Taking into consideration special populations, the incidence of chemobrain in pediatrics suffering from the most common forms of childhood cancers; acute lymphoblastic leukemia (ALL) and brain tumors ranges between 20–40 and 40–100%, respectively [76]. Chemobrain detrimentally complicates childhood cancer; survivors are less likely to marry, complete high school or maintain employment [77]. In the elderly, chemobrain was found to be even more pronounced due to the pre-existing cognitive decline associated with aging [78].

On the other hand, the "Theory of Unpleasant Symptoms (TUS)" is considered as a model for explaining cognitive impairment associated with standard-dose chemotherapy. This theory reveals the influence of physiological, psychological and situational factors (influencing factors) on symptoms (duration, distress, quality and intensity). These factors can affect the patient's level of performance (functional status, cognitive functioning and physical performance) [79]. As TUS is regarded as unidimensional measurement of unpleasant symptoms (i.e. influencing factors cause symptoms that finally affect patient's performance), the theory was updated to a revised theory that was used to explain the interaction between influencing factors [80]. Furthermore, the revised conceptual model of chemotherapy-related changes in cognitive function takes into consideration the antecedent events of cancer treatment and the meaning of the cancer diagnosis and relates the consequences of cognitive impairment to health-related quality of life [81].

Assessment of cognitive dysfunction in human subjects

Magnetic resonance imaging (MRI)

MRI is regarded as a powerful tool for assessing neuronal impairment as well as shedding light on the possible mechanisms underlying chemotherapy-induced cognitive dysfunction. Studies showed a persistent decline in neurocognitive functions 5 years after completion of chemotherapy [82]. Moreover, a study performed on breast cancer survivors, between almost 3 and 10 years after their chemotherapeutic treatment, set a linkage between the reduced grey matter density and lower functional MRI activation in certain brain regions and increased oxidative DNA damage in these regions [83]. Also, MRI demonstrated changes in white matter integrity in chemotherapy-treated patients. Since white matter is essential for the fast transfer of information between different brain regions, jeopardizing white matter to damage could lead to a difficulty in executing complex cognitive tasks [84].

Neuropsychological tests

Despite the growing body of evidence ensuring the importance of MRI in chemobrain assessment, the International Cognition and Cancer Task Force (ICCTF) declared that neuropsychological tests are regarded as the gold standard for assessing the cognitive functions [85]. Within this context, the following tests have been specifically recommended: the Hopkins verbal learning test-revised, Trail Making Test A and B, and Controlled Oral Word Association test. Although the ICCTF does not consider subjective patient reports as a reliable method in assessing chemotherapy-induced cognitive dysfunction, they are paramount in clinical practice and more likely to demonstrate the patients' diminished quality of life than objective tests that may not cover all of the patients' affected domains [86].

Electroencephalography (EEG)

Though EEG seems to be a quite useful non-invasive technique to evaluate the central effect of chemotherapeutic agents, its results are controversial, with studies showing a remarkable difference in neuronal activation intensity and latency in breast cancer survivors 5 years after being exposed to chemotherapy and others showing no significant difference in EEG recordings between cancer patients who received chemotherapy and untreated healthy controls [87, 88].

Positron emission tomography (PET)

It is a diagnostic and research tool available for many cancer patients. It uses a radiopharmaceutical 18-fluorodeoxyglucose (FDG) in imaging. This agent was used to examine cell metabolism and diagnose and manage different CNS disorders such as Alzheimer's disease, depression, epilepsy and Parkinson's disease [89, 90]. Lim et al. [89] revealed that glucose metabolism was decreased by chemotherapy in the medial prefrontal cortex and hippocampus that leads to cognitive impairment in animal models. Hurria et al. [91] used PET scans to measure changes in regional cerebral metabolism in evaluating the association between aromatase inhibitors treatment and cognitive impairment. In addition, Pomykala et al. [92] revealed the relation between pro-inflammatory cytokines, regional cerebral metabolism, and cognitive complaints following adjuvant chemotherapy for breast cancer using PET analysis.

Assessment of cognitive dysfunction in animal models

Animal models are regarded as an indispensable cornerstone in clinical research through providing the means to simulate human diseases, besides allowing elucidation of the underlying mechanisms and hence devising suitable therapeutic strategies that cannot be easily assessed in humans.

One way inhibitory/passive avoidance

Passive avoidance paradigm involves learning to inhibit the natural exploratory drive of rodents using an aversive electric foot shock. It can be assessed either step-down from a platform or step-through an electric door. Systemic administration of DOX has been shown to impair aversively motivated memory in various models [93, 94].

Contextual fear conditioning

It is the simplest version of fear conditioning in which only the context and the aversive stimulus presented as foot shock are paired. A very small dose of 1 mg/kg of DOX failed to cause any impairment in the contextual fear conditioning [95].

Contextual and cued fear conditioning

Animals are given pairings of a conditioned stimulus and an aversive electric foot shock. After an experimental-based delay time, rats are exposed to the same conditioning chamber and a differently shaped chamber with presentation of the auditory cue. Systemic administration of DOX caused a significant impairment in the contextual and cued fear conditioning task [45].

Morris water maze

In this task, animals learn to swim in a water pool made opaque using milk or white paint, navigable by external cues, until finding a submerged platform. Measured variables are mainly escape latency, number of crossings in that exact place, and the time spent per the target quadrant compared to the opposite one, swimming velocity and swimming path length [96]. DOX, in combination with cyclophosphamide, impaired spatial memory in female mice, a finding that persisted for several weeks after drug administration [97].

Novel recognition

Recognition is the process by which a subject is aware that a stimulus was previously encountered. It necessitates a series of cognitive operations that count on previously renowned information to match the observed event against the previously experienced ones. DOX treatment was found to impair both novel object and novel place recognition tasks in various models at different dosage levels [45, 46, 95].

Y-maze

This task utilizes rodents' natural exploratory behavior to assess spatial and recognition memory. DOX administration, in combination with cyclophosphamide, impaired spatial memory as evidenced by the alteration in rats' behavior in the Y-maze task [47].

Coping with chemobrain

Non-pharmacological strategies

Cognitive behavioral therapy (CBT)

CBT is a psychosocial intervention used to treat mental disorders via focusing on developing personal coping strategies to solve current problems and change unhelpful patterns of cognition, behaviors and emotions, hence reducing psychological and emotional disturbances [98]. Three studies in literature involved CBT techniques to assist chemobrain rehabilitation. The first study, single-arm pilot study, utilized memory and attention adaptation training (MAAT) intervention. Participants reported improvements in self-report of cognitive function amendment and improved quality of life. Furthermore, patients scored better in neuropsychological test post-treatment, and at the 2 and 6 month follow-up points [99].

The second study was a two-group; MAAT versus no treatment control, randomized clinical trial (RCT). Breast cancer survivors undergoing MAAT were assessed at baseline and post-treatment (8 weeks). MAAT participants made significant improvements relative to the control group on verbal memory and the spiritual well-being subscale of the Quality of Life-Cancer Survivors scale, but statistical significance was not achieved on self-report of daily cognitive complaints [100].

The third study assessed whether patients would report less cognitive decline after being treated via CBT for cancer-related fatigue using a secondary analysis of data from a randomized control trial. Cancer patients suffering from severe fatigue received 6-month CBT intervention focusing on the identification of the causative and perpetuating factors underlying fatigue. As a result, CBT participants experienced significantly lesser cognitive distress [101].

Neuropsychological/cognitive training intervention

Neuropsychological training is similar to CBT except that it gives more attention to memory, reasoning, and processing speed rather than on behaviors and emotions [102]. RCT assessed the efficacy of an online cognitive training program that encompassed 48 sessions. The intervention was designed to improve executive functions including cognitive flexibility, attention, multi-tasking, working memory, processing speed, planning and verbal fluency. The intervention led to significant improvements in executive functioning even in long-term cancer survivors [103].

Physical activity (exercise)

Extrapolating from aging and other comorbidities, exercise seems to amend cognitive functions with resistance training linked to an increased expression of brain neurotrophic and neuroprotective factors. Exercise was also found to augment hippocampal neurogenesis process, hence increasing hippocampal volume [104]. Animal model of chemotherapy-induced cognitive dysfunction showed that post-treatment exercise ameliorated the cognitive impairment and prevented chemotherapy-mediated-suppression of the neurogenesis process [105].

A recent RCT conducted in 479 cancer patients showed that a 6-week exercise program during chemotherapeutic treatment resulted in enhancement of self-perceived cognitive functions scores along with reduction of inflammatory mediator levels [106]. The relationship between exercise, cardiorespiratory fitness and cognitive functioning was assessed in breast cancer patients exposed to DOX-containing chemotherapy. The study compared physical aerobic fitness and self-reported physical activity with neuropsychological tests in patients and healthy control subjects. A significant correlation was detected within visual memory aspects [107].

Pharmacological treatment

Currently, there are no validated treatments for chemotherapy-induced cognitive impairment. However, few studies have converged on correcting the resultant cognitive deficits or blocking neurotoxic trajectories prompted by chemotherapeutic treatment. These include the following.

Modafinil

Modafinil is a stimulant approved by the FDA for the treatment of narcolepsy, to promote wakefulness. Kohli et al. [108] assessed the effect of modafinil on cognitive decline as a secondary study of a previous trial conducted to determine modafinil efficacy in attenuating cancer-related fatigue. Modafinil significantly improved memory processing speed and episodic memory compared to the placebo group [108]. Another double-blinded randomized crossover trial examined the modulatory effect of modafinil on cognitive function against placebo using trail making tests, Edmonton Symptom Assessment System and finger-tapping test. Modafinil significantly improved cognitive performance compared to placebo besides reducing depression and drowsiness [109].

On the contrary, Blackhall et al. [110] conducted a pilot study to assess the effect of modafinil on cancer-related fatigue and cognitive dysfunction. Modafinil treatment ameliorated fatigue and improved quality of life; however, it was not associated with improvement in cognitive functions [110].

Methylphenidate

Given the possible implication of imbalanced catecholamine levels in chemotherapy-induced cognitive dysfunction, medications that augment catecholaminergic tone may assist treating the resultant cognitive problems. Methylphenidate, a dopaminergic and noradrenergic agonist that reduces dopamine uptake at synapses and inhibits monoamine oxidase enzyme, has been extensively assessed within the setting of chemotherapy-induced cognitive dysfunction. In a randomized, placebo-controlled, double-blinded trial, Mar Fan and colleagues 2008 investigated the effect of methylphenidate on cognitive function and fatigue in fully resected breast cancer patients undergoing chemotherapeutic treatment. However, the study failed to find any statistically significant difference in cognitive function between methylphenidate and placebo-treated groups [111].

On the contrary, a randomized, double-blinded trial among pediatric cancer survivors, suffering from academic achievement problems and attention deficits, showed a

significant improvement within the attention aspect; however, no difference was noticed in verbal memory [112].

Donepezil

Donepezil is a centrally acting anti-cholinergic agent used mostly in the treatment of Alzheimer's disease. Since hippocampal-dependent memory loss is a potential reason underlying chemotherapy-induced cognitive dysfunction, donepezil may augment cognitive function when used in these patients. Donepezil prevented the cognitive dysfunction mediated by chemotherapeutics in animal model, with the animals' performance being exactly comparable to the control group [113].

A randomized, double-blinded, placebo-controlled clinical trial was conducted among breast cancer survivors who received adjuvant chemotherapy 1 year ago and currently suffering from chemobrain. The donepezil group performed significantly better in verbal memory aspects; however, there was no significant difference in other cognitive or subjective measures [114].

Fluoxetine

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) that is used mainly in depression treatment. Studies have previously shown that fluoxetine improves memory function in various neurodegenerative disorders via increasing the level of BDNF and promoting hippocampal neurogenesis, which are two mechanisms that possibly contribute to the pathogenesis of post-chemotherapy-induced cognitive dysfunction [45, 115, 116]. Fluoxetine precluded chemotherapy-induced cognitive dysfunction in several animal models as evidenced by the improved performance of animals within novel recognition tasks and T-maze task [117, 118]. Importantly, using SSRI during chemotherapy may not be favorable because of the overwhelming side effects experienced by a substantial subset of the subjects that may have sometimes led to termination of the study [117, 119].

Antioxidants

Antioxidative treatment would be a promising strategy because it mainly focuses on blocking the neurotoxic trajectories prompted by chemotherapeutic treatment, rather than focusing on correcting the resultant impairment. Several preclinical trials have shown that antioxidant treatment precluded chemotherapy-induced oxidative stress and cognitive impairment. Administration of γ-glutamyl cysteine ethyl ester prior to DOX significantly reduced brain oxidative stress in terms of diminished protein oxidization and lipid peroxidation. Since behavioral studies were not conducted, it is unclear whether these changes were concomitant with a corresponding improvement in cognitive status [22].

Xanthone derivative of garcinia mangosta also prevented DOX-mediated oxidative stress in brain tissue as evidenced by diminished production of protein carbonyl, nitrotyrosine and 4-hydroxy-2′-nonenal-adducted proteins in brain tissue [57]. Similarly, treatment with N-acetyl cysteine during the course of DOX-containing chemotherapy effectively aborted memory impairment observed in passive avoidance paradigm [120]. Ramalingayya et al. [121, 122] recently reported that the administration of either rutin or non-hypoglycemic dose of insulin mitigated brain oxidative stress and reversed memory deficits observed in behavioral tasks. In our previous work, astaxanthin (AST), a natural carotenoid with potent antioxidant capacity, offered neuroprotection against DOX-induced chemobrain. AST effectively prevented DOX-induced memory impairment as evidenced by the step-through passive avoidance test, restored hippocampal histological architecture and halted the oxidative and inflammatory insults induced by DOX [38].

Of importance, while any of the aforementioned pharmacotherapies may be extreme effective in guarding against chemotherapy-induced cognitive impairment, their impact on the anticancer activity of chemotherapeutic regimens still needs to be evaluated. In addition, clinical trials or studies are further warranted to be more defined for cancer type and address the chemotherapy class used. Clinical Imitations may be attributed to performing the majority of studies on one type of cancer (breast cancer), in relatively small number of patients ending in statistical discrepancy, thus hampering conclusive remarks. Furthermore, the management of cancer therapy differs from patient to patient as the response to therapy and side effects differ between them, a fact that demands further extensive evaluation.

Conclusion

Clinical studies conducted so far and animal models provided compelling proof that chemotherapy induces cognitive deficits. The possible mechanisms underlying the chemobrain phenomenon include oxidative damage, neuroinflammation, dysregulation of apoptotic and autophagic machinery, reduction in the level of neurotransmitters, inhibition of neurogenesis and manipulation of key kinase enzymes, in addition to genetic and epigenetic factors. While currently there is no validated treatment for chemotherapy-induced cognitive deficits, behavioral rehabilitation appears to improve the survivors' quality of life. Furthermore, several pharmacological agents have managed to show a promising effect in blocking the neurotoxic pathways; however, their impact upon the antineoplastic effect of chemotherapeutic regimens still need to be evaluated.

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