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**Review**

# Post-chemotherapy cognitive impairment in hematological patients: current understanding of chemobrain in hematology

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**Abstract**

**Introduction:** Cognitive impairment caused by chemotherapies, a condition known as chemobrain, is a possible side effect that affects alertness, learning, memory, and concentration.

**Areas covered:** Chemobrain has been principally investigated as possible side-effect among cancer patients. However, numerous drugs used to treat hematological malignancies can determine the appearance of chemobrain. In this review we have examined some commonly used drugs for the treatment of hematological malignancies which are known to have a deleterious action on cognitive functions. Numerous mechanisms have been suggested, comprising the direct neurotoxicity of chemotherapeutic drugs, oxidative stress, genetic predisposition, cytokine provoked damage, histone modifications, immune alteration, and the action of chemotherapeutic on trophic factors and structural proteins of brain cells.

**Expert commentary:** Cognitive dysfunction provoked by the treatment of hematological diseases is an actual challenge in clinical practice. Actually, there are no totally efficient and innocuous treatments for this syndrome. It is important that further investigations specify the existence of predictors and gravity factors to pre- and post-therapy cognitive change and identify the influence of tumor treatments on the cognitive alterations in long-term, cancer survivors. Moreover, future studies are needed to analyze the interactions between genetic risk, amyloid accumulation, intrinsic brain networks and chemotherapy.

**Key words**

Chemobrain; chemotherapy; cognitive impairment; hematological diseases; oxidative stress; cytokine.

**Article highlights**

- Cognitive impairment caused by several tumor therapies is a possible side effect
- Chemobrain affects learning, memory, processing speediness, and concentration
- Several mechanisms have been proposed such as oxidative stress, genetic predisposition, cytokine action, and immune alteration
- In this review we reported the future perspectives on therapy options for chemobrain

## 1.0 Introduction

### 1.1 General considerations on chemotherapy induced cognitive impairment

Cognitive impairment caused by several tumor therapies, a condition known as chemobrain or chemo fog or *chemotherapy induced cognitive impairment (CICI)*, is a possible side effect that affects alertness, learning, memory, processing speediness, concentration, and executive function [1-4]. In a recent meta-evaluation Lindner et al. evaluated 44 studies investigating the cognitive performance of adults treated with chemotherapy for non-central nervous system malignancies. Cognitive impairments were found in verbal memory, immediate free recall, delayed memory, delayed recognition memory, selective attention, and attention capacity [5].

CICI has been described in up to 6-75% of subjects [6,7]. However, the true entity of chemobrain is uncertain. It remains quite difficult to identify, due to an absence of a uniform description and technique of cognitive evaluation, the multiplicity of chemotherapies, the existence of confounding elements such as associated therapies, and due to host-related elements such as age, educational level, menopause. Moreover, the occurrence of relevant cognitive impairment before therapy is observed in about 30 % of leukemia subjects [8].

Although such CICI is generally mild, it occasionally prejudices actions of daily living and quality of life. Moreover, CICI could possibly alter their compliance, eventually influencing their medical managing [9]. Alterations are short-term in the greater part of subjects but have been described to continue for months or even years in about 35% of subjects in remission [10]. Data from the International Cognitive Workshop proposed that CICI may be a long-term effect and has been described to persist 5–10 years after therapy [11-13].

Cancer is an age-related disease as well as cognitive decline, which is why brain aging is a predisposing factor for chemobrain. Due to the increase in aging population and the incidence of tumors, the phenomenon of chemobrain will be increasingly frequent.

However, conflicting data are present in the literature, and the role of chemotherapy neurotoxicity for cognitive alteration has been doubted by findings of cognitive decline in subjects whose systemic chemotherapy had not yet started or who were controlled without chemotherapy. Several results have linked pretreatment cognitive damage to inflammatory processes provoked by the cancer. Probably, effects of having tumor on cognitive function are to be expected even if no adverse effects of chemotherapy were to occur. It seems very likely that sleep problems, distress, and pro-longed sick leave, among other factors associated with having tumor, influence the brain, which, as a plastic and highly dynamic organ, is vulnerable to all subtly changes in interaction with it [14, 15].

**2.0 CICI in hematological patients**

CICI has been principally investigated as possible side-effect among women undergoing treatment for breast cancer, whereas only few studies have investigated hematological patients. However, numerous drugs used to treat hematological malignancies can determine the appearance of CICI.

In the next paragraphs we examine some commonly used drugs for the treatment of hematological malignancies which are known to have a deleterious activity on cognitive functions (Table 1).

Adriamycin (ADR) is a usually utilized chemotherapeutic drug for the treatment of leukemia. As reported by immunohistochemical, histological, and morphometric procedures it can provoke CICI [16].

Studies have demonstrated that ADR therapy augments the vulnerability of brain mitochondria to oxidative stress, causing deterioration and death of brain cells. Moreover, ADR can alter normal nontumoral cells that might participate in chemotherapy-induced cognitive deficits [17].

A similar action seems to be carried out by Doxorubicin (DOX), a derivative of ADR, a drug frequently employed in multiagent chemotherapy protocols to cure leukemias. DOX has been shown to intercalate into DNA and augment the generation of reactive oxygen species (ROS) and block cellular proliferation. DOX and its main metabolites do not traverse the blood brain barrier (BBB), yet CICI is often described. Experimental investigations performed in an animal model have demonstrated that DOX stimulates a relevant increase of CNS oxidative stress, confirmed by augmented concentrations of protein and lipid oxidation in the brain. Successive studies have demonstrated that DOX has an indirect toxic effect on the central nervous system (CNS) resulting from an augment of the plasma Tumor Necrosis Factor (TNF) alpha which penetrates through BBB. Research suggests that plasmatic TNF alpha is generated for the oxidation of APOA1 by DOX which in turn augments TNF alpha generation by macrophages [18,19].

Drugs used in diseases other than acute leukemia may also have a negative effect on cognitive functions. Mitoxantrone (MTX), is an anticancer drug employed in the therapy of acute myeloid leukaemia and non-Hodgkin's lymphoma (NHL); whereas in combination protocols, it is used in the remission-induction therapy of blast crisis in chronic myeloid leukaemia.

Modest data is existing about MTX supposed neurotoxicity. However, MTX was demonstrated to provoke greater cytotoxicity than DOX in differentiated SH-SY5Y cells. MTX provoked greater morphological harm, with inferior cell density and neurites loss. Both drugs provoked signs of apoptosis, especially MTX. The mechanisms implicated seem diverse among the two drugs. The high potential toxicity of MTX may be caused by its greater lipophilicity, that simplifies the absorption of the drug into the cells [20].

Methotrexate is an antimetabolite agent that is widely used in treating leukemia and lymphoma. Numerous studies demonstrate that high-dose intravenous administrations of methotrexate decrease spontaneous activity and reduce startle response to noise in animals [21,22]. Furthermore, intraperitoneal administration of methotrexate increase the onset of seizures in mice and cause an alteration of long-term memory [21].

The combination of chemotherapy and CNS-directed radiation treatments seem to provoke frequent and serious neurologic damages [23]. For this reason, methotrexate should not be used after brain irradiation. In any case a cognitive assessment should be made in therapeutic protocols using radiotherapy and chemotherapy.

In B-cell NHL patients treated with bendamustine and rituximab, Zimmer et al. utilized objective and subjective measures of cognitive functions in combination with serum factors and neuroelectric recordings. Self-perceived status of cognition, fatigue and emotional functioning were evaluated in 30 patients and in 10 healthy controls. Cognitive activity was found altered if compared to normal subjects [24]. CICI was more serious in subjects treated with bendamustine and rituximab (R) than in subjects who received R in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP). Interleukin-6 (IL-6) and serum brain-derived neurotrophic factor (BDNF) might be implicated in the pathogenesis of CICI in these patients [24].

Lenalidomide (Len), a new analogue of thalidomide, has been used in multiple myeloma patients and myelodysplastic subject. Its anti-angiogenic and immunomodulatory actions, although analogous to thalidomide, do not seem to present the same grade of neurotoxicity. Lesser degrees of chemotherapy-caused peripheral neuropathy are reported. A death in a Phase III trial of 176 Len-treated MM subjects was attributed to leukoencephalopathy [25]. Rollin-Sillaire et al. described two subjects in whom cognitive impairments arose or has significantly worsened over the course of Len therapy. Within the first month of the Len therapy, both patients showed neuropsychological symptoms and alterations in the ability to perform activities of daily living (ADLs). Severe episodic memory impairment - the capacity to acquire and remember new data - was observed in both patients. The alteration was demonstrated in both cases by poor performance in the Free and Cued Selective Reminding Test. Furthermore, the subjects presented also signals of a significant alteration in occupational and social functioning [26].

The possible mechanism by which Len may influence cognitive function is yet unknown. An anti-angiogenic action might alter neurogenesis in hippocampal structures. However, it is not known to what extent Len can traverse the BBB into the CNS or if its actions are due to a systemic effect. In any case there are two studies on the remission of CNS hematologic malignancies after Len therapy which could indicate that Len may be able to cross a damaged BBB [27-29].

The interferon family comprises INF-a, INF-b, and INF-g, and represents a composite group of cytokines with antiviral, oncologic, and immunoregulatory activity. The most frequent CNS side-effects consist of cognitive slowing, somnolence, personality changes, and headache. Movement disturbs, mania, depression, visual dysfunction, and several other neuropsychiatric disorders can also occur. These psychiatric and neurologic side-effects seem to be dose-related and are more frequent in elderly subjects and in those with underlying brain alterations. However, symptoms usually decrease after suspension of the drug [30].

Platinum-based anti-cancer drugs, such as cisplatin, have been demonstrated to modify the exocytosis of catecholamines, a group of CNS neurotransmitters implicated in neurological activities. The discharge of serotonin and dopamine from coronal brain slices taken from rats after intravenous administration of platinum-derived was analyzed with fast-scan cyclic voltammetry [31]. Platinum-based therapy can alter serotonin and dopamine release even if it has no effect on their uptake and reserve pool [32]. Mohammadi et al. reported that cisplatin causes cell apoptosis via lipid alterations [33]. Authors employed time-of-flight secondary ion mass spectrometry to evaluate the action of cisplatin. Principal components analysis demonstrated that cisplatin therapy of PC12 cells drastically alters the presence of diverse lipids and their derivatives, especially phosphatidylcholine and cholesterol, which are reduced. Lipid modifications provoked by cisplatin therapy at the cell surface are related to the molecular signaling pathways of cisplatin-provoked apoptosis of cells [33].

Moreover, Dietrich et al. found that cisplatin, and cytosine arabinoside are more toxic for the progenitor cells of the CNS and for nondividing oligodendrocytes than they are for several cancer cell lines. Augmentation of cell death and suppression of cell division were seen in vivo and in vivo. When administered in mice, these substances provoked cell death and reduced cell division in the subventricular zone, in the dentate gyrus of the hippocampus and in the corpus callosum of the CNS, and in the subventricular zone. In some cases, this effect persisted for weeks after drug administration terminated [34].

Antibodies blocking Cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), Programmed cell death 1 (PD-1) and Programmed cell death ligand 1 (PD-L1) have arisen as novel immunotherapeutic drugs in several hematological tumors. These immune checkpoint inhibitors (ICIs) can probably provoke autoimmune disorders, comprising neurological syndromes that can implicate all areas of the CNS [35]. However, in a recent study, adult cancer subjects starting a therapy with ICIs were examined by a neurologist before the start of ICIs (baseline) and three months later. Neurological examination studied mental status, cranial nerves, motor function, sensitive function, reflexes, coordination, gait. For cognitive functions they used two different tests: MoCA7, and TNI-93. However, in this small series of subjects treated with nivolumab or pembrolizumab (10 patients) no sign of cognitive impairment was detected during the treatment [36].

**3.0 Mechanisms of chemotherapy-related cognitive dysfunction**

It seems that “chemobrain” has common pathological features with Alzheimer’s disease (AD) comprising behavioral changes such as depression and working memory deficits as well as synaptic deficits and neuroinflammation [37].

In the previous section we mentioned some of the possible mechanisms by which drugs used to treat hematological malignancies can exert a neurotoxic action. We will now evaluate in detail all the processes able to provoke the onset of CICI in patients treated with chemotherapy [Fig.1].

Unfortunately, the potential mechanisms of chemotherapy-related cognitive dysfunction are inadequately understood. However, various mechanisms have been suggested, such as direct neurotoxicity of chemotherapeutic drugs, oxidative stress, genetic predisposition, cytokine provoked damage, histone modifications, immune alteration and shortened telomeres [10,38].

One suggested mechanism could be constituted by a direct harmful action exerted by the drugs against the CNS [1]. Studies performed using magnetic resonance imaging have shown that patients with CICI have a more evident alteration in the white matter than in the gray compared to control subjects. [39, 40].

Numerous experiments have demonstrated that chemotherapy affects gliogenesis, neurogenesis, and myelin fibre integrity causing memory alterations and learning difficulties in chemotherapy-treated animals compared to controls [41].

Moreover, reductions of the progenitor cell pool and alteration of the functionally postnatal production of new neural cells suggests a possible explanation for the cognitive side effect profile seen in several subjects treated with chemotherapy. Arresting new cell production in the central nervous system should provoke cognitive damages that localize neurologically to the hippocampus and subcortical white matter, causing impairment of verbal and visual episodic memory function [42].

However, drug action on the BBB permeabilization could be of great relevance. In fact, drugs administration could provoke relevant changes in the cytoskeletal and junctional apparatus of endothelial cells (EC), thus decreasing their tightness.

EC have been determined to have a central role in BBB properties as they are the anatomic basis of the barrier. These cells are different to other vascular endothelia in their ability to control the migration of molecules to and from the neural parenchyma. It is well known that the capillary endothelium in the brain is tougher than in peripheral microvessels, whereas the cytoplasm has a homogenous width with no *fenestrae*.

Some of the drugs used for the treatment of hematological malignancies may cause EC alterations able to provoke BBB interruption or dysfunction. Augmented cerebrovascular permeability can be obtained via transcellular or paracellular route [30]. Numerous molecular mechanisms contribute to the alteration of interendothelial junctions, such as free radicals, inflammatory factors, bradykinin, and angiogenic factors. These elements, strongly associated to CICI, can cause a downregulation of junctional proteins, cytoskeletal modifications and a direct alteration of interendothelial junctions.

By employing a rat brain endothelial cell line Branca et al. studied the signaling pathway that ensued the entrance of oxaliplatin within the cell. They reported that the administration of oxaliplatin provoked modifications of the tight junction proteins zonula occludens-1 and of F-actin [43].

However, since most chemotherapeutics are unable to overcome BBB, it is likely that many of the neurotoxic effects exerted by these drugs imply a systemic mechanism.

It is now definitively established that chemotherapy generated pro-inflammatory cytokines are capable to traverse the BBB and cause inflammation in brain [44]. Cytokines traverse the BBB by passive diffusion [45] or via receptor-mediated endocytosis [46].

In aged people, augmented pro-inflammatory cytokines are connected to reduced learning ability and cognitive deterioration [47-49]. Proinflammatory cytokines are able to damage neuronal cells [50], and numerous reports have demonstrated that greater blood levels of IL-6 were related to worse cognitive abilities, while the increased concentration of IL-4 was protective against cognitive impairment in tumor subjects [51,52]. TNF-α was also related to memory disorders in tumor survivors [53]. Moreover, different reports described superior cognitive performance in IL-6 deficient animals, validating the negative actions of the cytokine [51-54]. Finally, neuroimaging investigations have corroborated the supposition that chemotherapy-caused cytokine alteration in specific brain zones may cause the onset of chemobrain [55].

In a research paper, animals were given intraperitoneal docetaxel, ADR, and cyclophosphamide (DAC). The DAC-treated animals had lower cognitive performance than the control animals and presented a clear reduction of the magnetic resonance signal intensity in the hippocampal subregions. In a different analysis, in which transcranial two-photon imaging was employed, DAC significantly reduced dendritic spines in the medial prefrontal cortex. Moreover, chemotherapy caused a relevant augment in the concentrations of inflammatory cytokines such as IL-6 and TNF-α and a remarkable reduction of the concentrations of anti-inflammatory cytokines such as IL-4 and IL-10 both evaluated in the sera and in the brain. The concentrations of inflammatory cytokines revealed an inverse correlation with the cognitive performance and with the hippocampal magnetic resonance signal intensity, and a direct correlation with spine loss [55].

Yet another study reported a possible epigenetic mechanism for CICI. As seen above hippocampal cell growth has been involved in memory and learning. The processes that regulate memory necessitate the coordinated action of transcription factors and several coregulators that control chromatin structure. The enzymes involved are the histone acetyl-transferases and the histone deacetylases [56, 57]. Chemotherapeutics can negatively regulate the proliferation of neural progenitor cells and chromatin remodeling in the hippocampus, with augmented histone acetylation and reduced histone deacetylase action [58].

The more relevant mechanism for the commencement of chemobrain is likely represented by the modification of the oxidative equilibrium. In fact, the oxidative stress is the most frequent etio-pathological element conducting to substantial neurobiological modifications. Butterfield describes that anti-neoplastic drugs produce superoxide free radicals which in turn oxidate apolipoprotein A1. Apolipoprotein A1 augments TNF alpha levels, and the cytokine alpha operates on its receptors situated on BBB (p55 and p75) and then arrives at the brain where it provokes neural death [59]. However, it is relevant to observe that numerous oncohematologic diseases show an altered oxidative stress [60-64 and a considerable number of chemotherapeutics operate by causing oxidative stress in tumor tissue as well as in the brain.

In brain tissue, morphological modifications indicative of oxidative stress damage after chemotherapy, are characterized by alterations in neuronal dendrites, and spine density [65]. In any case the brain is particularly sensible to the damage caused by ROS since the brain is an enormous oxygen consumer (20% of the body consumption) and has a small concentration of protective antioxidant systems.

The brain holds elevated concentrations of iron and a great quantity of polyunsaturated peroxidizable fatty acids that operate as pro-oxidant and could causes autophagic cell death. Moreover, lipid peroxidation provokes the generation of substances such aldehydes which may also initiate neuronal apoptosis.

Important might also be the action of chemotherapeutic on trophic factors and structural proteins of brain cells. BDNF can cause the growth of neuronal stem cells and to sustain the survival of neurons. Furthermore, augmented BDNF concentrations are correlated with augmented long-term potentiation [66]. Chemotherapeutics block the production of BDNF, thus causing detrimental actions on hippocampal functions such as memory and learning [67].

In a cross-sectional study, Natori et al. have recently examined the concentrations of the high-molecular-weight neurofilament subunit (pNF-H), a central protein in central axons, in tumor subjects before and after chemotherapy. The data demonstrated a dose dependent increase of the pNF-H concentration [68, 69].

Moreover, based on the crucial role of the hippocampus for preservation of brain plasticity through life, numerous experimental researches have analyzed the effects on hippocampal neurogenesis. In fact, data from both animal models and neuroimaging studies suggests a possible relationship between chemotherapy provoked hippocampal damage and neurocognitive alterations detected in cancer subjects after chemotherapy [70].

However, we must also consider that some therapies are able to hasten normal aging processes, such as the shortening of telomeres, which relates to neuronal apoptosis [71].

An additional factor to evaluate is that the sensibility to cognitive modifications during and after chemotherapy may be due to host genetic factors, such as SNPs implicated in cerebral activities or inflammation [72, 73]. For instance, APOE polymorphism affects the metabolism of amyloid -beta, which is accumulated in the brain and is a central factor in the age-related cognitive decline. Moreover, the same tumor treatment may augment amyloid-beta storage via a modified glucose metabolism, inflammation and oxidative stress. A recent research demonstrated that the epsilon- 4 allele of APOE may be a possible indicator for augmented sensibility to CICI [73]. Contrary, polymorphisms of the BDNF-gene have been connected to neuroprotection of chemotherapy-related negative actions [74].

Other probable mechanisms could be the action of chemotherapeutic drugs on the brain activity. Chemotherapy disturbs theta activity in the adult brain (3–12 Hz), and it is well known that theta activity stimulates effective learning in humans and mice [75]. Moreover, of great relevance could be the inadequate estrogen-related defense of brain cells following chemotherapy- or otherwise- provoked menopause [76,

77], and a modified cerebral blood amount through blood vessel alteration [78] and/or chemotherapy-provoked anemia [79].

Finally, a novel mechanism could be the decrease of the default mode network (DMN) [80]. It is surely recognized that dedicated brain zones do not work in isolation but collaborate in networks which are synchronized with specific zones participating in a context-specific manner [81-83]. Chemotherapeutics seems able to alter DMN [80].

**4.0 Diagnosis of CICI**

CICI has been diagnosed employing neurological test batteries, evaluating memory, processing speed, and attention [84]. In a meta-analysis Authors included 13 works across five tumor types comprising leukemia and lymphoma. The examined domains were: concept formation and reasoning, memory, verbal functions and language skills, construction, orientation and attention, executive functions, and perception. Verbal functions and language skills were assessed by several tests comprising the Controlled Oral Word Association Test WRAT-III, the Reading Sub-test, and the Boston Naming Test. The memory domain was evaluated via the California Verbal Learning Test, and the Logical Memory and Family Pictures from the WMS-III. The cognitive domain of construction was studied with the WAIS-III Block Design, the Folstein Mini Mental State Examination, and the Repeatable Battery of Adult Neuropsychological Status. WAIS-III Digit Symbol, Stroop Colour and Word Testand the Trail Making Test were used to evaluate orientation and attention. The cognitive domain of reasoning and concept formation comprised the WAIS-III Arithmetic and Wisconsin Card Sorting Test. Tests that assessed executive functions included the Intradimensional Extradimensional Shift Task, WAIS-III Coding and the Highly Sensitive Cognitive Screen. Finally, the cognitive domain of perception was evaluated by tests such as Test of Facial Recognition and Letter Cancellation.

It is possible that CICI is best recognized employing individual exams within a cognitive domain compared with task batteries employing a multifactorial score. Individual test data are more mutable in patients, reaching more frequent significant results.

Functional magnetic resonance imaging (fMRI) analyses studying modifications connected with cerebral blood flow dependent blood oxygenation concentration, have demonstrated that tumor subjects have a diverse CNS activation modality through declarative memory tasks. Moreover, advanced neuroimaging studies can help to clarify the effects of chemotherapy on brain structure and function. Specifically, magnetic resonance imaging (MRI) has been increasingly used to characterize changes within particular brain regions, such as on gray matter, white matter and hippocampus [85-87].

However, it is necessary to consider that the links between subjective complaints and objective performance in patients are rather weak. Actually, neuroimaging studies have more significance in research than a diagnostic value. In any case neuroimaging data are not useful to study a single patient.

Baudino et al. described relevant modifications in glucose metabolism in numerous zones after treatment. The modifications were more relevant in the frontal lobes, where the metabolic alteration was proportionate to the quantity of chemotherapeutics [88]. The interpretation of the results must however be prudent in consideration of the small number of patients examined (only 50 adult cancer patients with diagnosis of lymphoma: 18 patients were studied prior and 32 after to chemotherapy).

A different study investigated brain glucose metabolism in subjects with Hodgkin disease (HD) before and after treatment. After the administration of DOX, bleomycin, vinblastine and dacarbazine (ABVD) treatment, patients underwent 1 positron emission tomography (PET)/computed tomography brain scans, both baseline (PET0) and interim (PET2). A number of subjects were also evaluated after four additional cycles (PET6). Furthermore, a control group of chemotherapy-naïve subjects was enrolled. The principal result of the study was a significant hypometabolism in OFC bilaterally (BA11) and in the left ACC (BA32), and an augmented glucose consumption in the right parietal cortex, in HD patients after the first two CHT cycles. These modifications receded at the end of the treatment, six months after diagnosis [89]. However, the lack of a neuropsychological or psychiatric evaluation following disease diagnosis and during treatment is an evident limitation of this study.

**5.0 Future perspective on treatment options for CICI**

At present, there are no totally efficient and innocuous treatments against CICI [7]. Most memory enhancers existing have relevant side effects or inadequate effectiveness in tumor subjects. For instance, donepezil, a pro-cholinergic drug, has been experimented at the preclinical level, but the efforts in demonstrating efficacy in human subjects have been vain [90, 91].

Numerous researches have been conducted on the prevention and the therapy of Dox induced CICI [Fig.1]. Therefore, it is possible to distinguish different drugs that act with different mechanisms on neuroprotection.

**5.1 Effects on oxidative stress, neuroinflammation and acetylcholine activity**

Tea polyphenols are well-known chemopreventive substances. Cheruku et al. valued the neuroprotective capacity of catechin hydrate (catechin), a tea polyphenol, in IMR-32 neuroblastoma cells in vitro. Moreover, they studied the mitigation of memory deficit in Wistar rats in vivo after administration of DOX [92]. These studies showed catechin increased percentage viability of undifferentiated IMR-32 cells. Catechin treatment also demonstrated an increase in neurite length of differentiated cells. In vivo neuroprotection of catechin was studied employing new object recognition task in time-induced memory deficit model at different doses. Catechin demonstrated a significant reduction of time-induced memory deficit in a dose-dependent manner. Furthermore, it caused an important reduction of oxidative stress, acetylcholine esterase and neuroinflammation in the hippocampus and cerebral cortex [92].

Acceptable results have been obtained using other substances of natural origin. Astaxanthin (AST), a naturally occurring carotenoid, is known for its antioxidant, antiapoptotic, and anti-inflammatory activities. El-Agamy et al. studied the neuroprotective and memory-enhancing actions of AST against DOX-induced behavioral and neurobiological alterations. AST therapy considerably protected against DOX-caused memory alteration. Furthermore, AST repaired hippocampal histopathological architecture, reduced DOX-caused oxidative insults, and decreased the augment in acetylcholinesterase activity [93].

It is also certainly interesting that DOX subjects not treated with 2-mercaptoethane sulfonate (MESNA) at the same time, presented a relevant increase of plasma protein-bound 4-hydroxynonenal, while patient who had been coincidentally treated with MESNA did not, indicating that simultaneous administration of the antioxidant MESNA with DOX avoid oxidative stress. Aluise et al. reported that MESNA reduced DOX-caused oxidative stress, and also reduced DOX-induced augment of TNF-α concentrations. These data could indicate that MESNA could decrease systemic and neurologic side effects provoked by Dox [94].

Vitamin D (VitD) is known to contribute to the control of CNS homeostasis [76]. Reduction of NO and inflammatory cytokines comprising TNF alpha and IL-6 by 1α,25(OH)2 VitD3 was demonstrated in activated microglia [95]. These data suggest that VitD additions in diet could augment the protection in brain against CICI-related local inflammation. This method could have importance to those subjects undergoing chemotherapy who reside in northern regions.

Finally, resveratrol, a natural polyphenol present in fruits and plants, has nootropic, immunomodulatory, and neuroprotective actions. Resveratrol reduces neuroinflammation by increasing the generation of anti-inflammatory cytokines and blocking pro-inflammatory cytokine production. Resveratrol also safeguards neuroplasticity and regulates neurotrophic action [96-99]. Animals co-treated with resveratrol demonstrated lower concentrations of the proinflammatory cytokines such as TNF-α and IL-6, and higher concentrations of IL-4 and IL-10 in sera and brain tissues. Resveratrol regulates the cytokine-regulating pathway peroxisome proliferator activated receptor (PPAR)-γ/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and defends against the reduction of tropomyosin receptor kinase B, BDNF, and calmodulin-dependent protein kinase II. These data prove the capacity of resveratrol in blocking chemobrain.

As far other substances, Cotinine, the principal derivative of nicotine, a promising novel drug against Alzheimer disease, corrected visual and spatial working memory and reduced depressive-like behavior in animals treated with cyclophosphamide, methotrexate and 5-fluorouracil [100]. In fact, cotinine is a positive regulator of the α7 nicotinic acetylcholine receptor (α7nAChR), and this receptor is deemed a target for CICI [101, 102]. Activation of the α7nAchR is regulated by prion protein (PrPC) expression and has a neuroprotective effect by modulating autophagic flux.

### 5.2 Modification of p53

In a different attempt, stimulated by the supposition that neuronal mitochondrial dysfunction underlies CICI, Chiu et al. evaluated the effect of the administration of the small molecule pifithrin (PFT)-μ, an inhibitor of mitochondrial p53 accumulation, in blocking CICI. Male mice treated with cisplatin +/− PFT-μ were studied for cognitive function employing novel object/place recognition and alternation in a Y-maze. Cisplatin altered performance in the novel object/place recognition and Y-maze tests. PFT-μ administration prevented CICI. Remarkably, augmented mitochondrial p53 did not provoke a cerebral caspase-3 activation or cytochrome-c release. Moreover, PFT-μ administration did not reduce the antitumor efficacy of cisplatin [103].

### 5.3 Action on neuronal differentiation

A different therapeutic approach investigated the possible use of the mesenchymal stem cells (MCSs) derived from umbilical cord tissue. Several studies demonstrate that human umbilical cord MSCs could be stimulated to differentiate into neuron-like cells [104]. Zickri et al. evaluated the possible therapeutic action of human umbilical cord mesenchymal stem cells (HUCMSC) treatment on ADR-caused chemobrain in rats. ADR-related degenerative modifications were reduced by HUCMSC therapy. A mutual relation was reported between the degree of regeneration and the presence of undifferentiated mesenchymal stem cells [105]. Analogously, intrahippocampal transplantation of human neural stem cells reduced all cognitive alterations when mice were studied one month after the termination of chemotherapy. In transplanted mice, grafted cells lived and differentiated along neuronal and astroglial lineages. Improved cognition was due to a decreased neuroinflammation and increased host dendritic arborization [65].

Interesting results have been obtained using completely different substances. Metformin is widely used for therapy of type 2 diabetes. Treatment of mice with cisplatin causes cognitive deficits. Co-administration of metformin blocked these cisplatin-caused cognitive alterations [106]. Moreover, co-administration of metformin prevented all the structural anomalies in cisplatin-treated animals.

It was also demonstrated that metformin stimulates the differentiation of microglia towards an M2 suppressive/wound healing phenotype that could participate in metformin's positive actions on brain damage [107].

### 5.4 Other pharmacotherapeutic approaches

Recently, other substances have been proposed for the treatment of CICI, and in particular, methylphenidate and modafinil [108].

Methylphenidate is a dopaminergic and noradrenergic agonist influencing the fronto-striatal network that controls attention and is generally employed in the therapy of attention deficit hyperactivity disorder [109].

Modafinil is a CNS stimulant established as a first-line treatment for improving wakefulness in the context of narcolepsy. Modafinil acts primarily on hypothalamic sleep-regulating centers via the reduction of

gamma-amino butyric acid in the sleep-inducing preoptic area. This specific interaction with the sleep–wake cycle, as opposed to generalized excitation, might be the motive that modafinil is associated with fewer side-effects than other CNS stimulants such as methylphenidate [110].

Finally, pharmacotherapeutic approaches for tumor therapy-induced cognitive symptoms comprise drugs used in subjects with memory impairment (e.g., donepezil, memantine, and ginkgo biloba), and bone marrow supporting agents (egg, erythropoietin) [111-114]].

**5.5 Non-pharmacological approaches**

Attempts have been also made to cure alterations of cognitive functions without drugs.

Two large randomized controlled trials reported that an 8-week Mindfulness-based stress reduction program [115], and a 16-week Web-based cognitive rehabilitation program [116] significantly ameliorate self-reported and neuropsychological measures of cognitive performance in chemotherapy-treated tumor subjects. Furthermore, signs of anxiety, and depression significantly decreased, with a significant increase of their quality of life.

Similarly, physical activity has been reported to ameliorate patients' quality of life after chemotherapy [117,118]. Regular exercise has preventive actions in neurodegenerative diseases and has been reported to stimulate beneficial structural and functional modifications of the CNS, and improve cognitive performance [119]. Interestingly, the biggest trials in this theme consist of Asian-influenced exercise programs (e.g. yoga), although exercise suggestions for brain health indicate that aerobic exercise may be most effective [120]. Exercise provokes structural modifications and improves neurogenesis in the dentate gyrus of the hippocampus. These modifications have a central role in ameliorating hippocampus-dependent memory and learning. Investigations have demonstrated that aerobic exercise changes BDNF concentrations in the hippocampus, and thus may increase cognitive function [121].

However, current reports in the context of CICI and exercise are scarce and have numerous possible biases (insufficient control groups, absence of standardized valuations, inadequate measurement time points).

Dietary methods that adjust inflammation and neurogenesis are encouraging approaches for moderating CICI in tumor survivors. Omega-3 fatty acids dispensed contemporarily with DOX have been reported to block depressive-like behaviors and decrease oxidative stress, neuroinflammation, and neural apoptosis in mice. On the contrary, diets high in added sugars may reduce their anti-inflammatory action, reduce adult hippocampal neurogenesis, and augment cognitive deficits. A diet rich in marine-derived omega-3 fatty acids and low in added sugars may be a perfect model for improving neuroinflammation, thereby defending neurons from the toxic actions of chemotherapy [122].

## 6.0 Conclusion

CICI is an intricate, composite phenomenon that necessitates additional researches to obtain treatments and procedures that reduce its effect on quality of life [123].

Although there is no specific treatment to improve memory, it is possible to provide subjects with some coping procedures and recognize which particular part of the memory is altered and suggest rehabilitative exercises to accelerate recovery after therapy.

## 7.0 Expert opinion

Cognitive dysfunction provoked by hematological diseases or the treatment is an actual challenge in clinical practice. Assessing cognitive alterations in the elderly cancer population is a daily necessity, as it could influence the choice of the most appropriate therapy, including the use of oral drugs.

It is important that further investigations specify the existence of predictors and gravity factors to pre- and post-therapy cognitive change and identify the influence of tumor treatments on the cognitive alterations in long-term, cancer survivors. Some elements associated with the subject, like depression, may facilitate cognitive impairment, while the role of others, like educational level, remains to be specified. Models of aging may offer a conceptual framework to drive future studies.

Moreover, future studies combining APOE status, PET-based amyloid beta markers and MRI are needed to analyze the interactions between genetic risk, amyloid accumulation, intrinsic brain networks and chemotherapy. Future investigations should also explore the influence of multiple tumor treatments (e.g., radiation and hormone treatment) in greater detail [124,125].

A different field of potential research is constituted by the role played by the microbiota. Gut-brain axis dysfunction and microbiota dysbiosis have been studied as potential mechanisms of cognitive impairment. It will be essential to explain the role gut-brain axis dysregulation has in the chemotherapy setting, stressing peripheral-to-central immune signaling mechanisms and their involvement to neuroimmunological variations associated with chemotherapy exposure [126], the action of intestinal permeability, damage to nerves of the enteric and vagal and humoral mediated changes.

It will also be appropriate to evaluate not only the most serious cognitive alterations determined by the chemotherapeutic treatment. In fact, chemotherapy was found to be associated with elusive and transitory alterations, which were demonstrable only with neuropsychological testing and affected most particularly concentration, memory, and speed of information processing. Attention should be given to the pediatric patients. Neuropsychological abilities should be evaluated before, during, or shortly after the end of therapy. This will provide a baseline should the child's performance begin to decline. Difficulty with protracted school absences or trouble at school should activate neuropsychological evaluation. In this group of patients, few studies have addressed the benefits of interventional strategies but

methylphenidate, modafinil and erythropoietin, as well as rehabilitation in children, have shown encouraging results.

In vitro and in vivo studies will finally allow us to establish whether new therapeutic approaches will be able to attenuate the symptoms or reduce the duration of symptoms capable of nullifying the successes that the new drugs used in hematology have managed to achieve for the treatment of neoplastic pathologies.

In any case, future studies must have more consideration of the difficulties in reproducibility of results, small sample sizes, and (most importantly) the substantial difference between subjective reporting of impairment and the objective measurement of that impairment.

However, it must be clear that fear of developing cognitive alterations should not discourage the usage of potentially advantageous treatment, principally in settings in which chemotherapy treatment is lifesaving and not discretionary. However, for those survivors of hematological diseases who presently are unable to continue their pre-illness personal and professional occupations that necessitate attentiveness and concentration, we must act to find successful rehabilitation and treatment strategies that will better their outcomes.

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**Legend:**

Table 1. Commonly used drugs for the treatment of hematological malignancies which are known to have a deleterious activity on cognitive functions.

Figure 1 Potential mechanisms or risk factors and potential treatments or protective factors for chemobrain.

| Drug | Possible mechanism | Symptoms or brain damage | Ref. |
|---|---|---|---|
| Adriamycin | Oxidative stress | Death of brain cells | 17 |
| | | | |
| Doxorubicin | Oxidative stress<br>Increased TNFa levels<br>Mitochondrial dysfunction<br>Loss of choline-containing biomolecules<br>Decreased hippocampal cell proliferation | Cognitive impairment | 18, 19, 70 |
| | | | |
| Mitoxantrone | Cell apoptosis<br>Neurite loss<br>Epigenetic mechanism | Cognitive impairment<br>Impairment of memory acquisition and retention | 20, 58 |
| | | | |
| Methotrexate | IL-6<br>Serum brain-derived neurotrophic factor<br>Decreased hippocampal cell proliferation | Acute (reversible), subacute or chronic encephalopathy<br>Seizure | 24, 70 |
| | | | |
| Lenalidomide | Antiangiogenic action | Cognitive impairment | 25, 26 |
| | | | |
| IFN | Unknown | Cognitive impairment | 30 |
| | | | |
| Cisplatin | Serotonin<br>Dopamine<br>Action on CNS progenitors | Cortical blindness<br>Seizures<br>Cell apoptosis | 31-33 |
| | | | |
| Check points inhibitors | Autoimmune disorders? | To verify | 36 |

**Table 1 Commonly used drugs for the treatment of hematological malignancies which are known to have a deleterious activity on cognitive functions.**

Figure 1