

Chemotherapy and cognitive function: comprehensive review on Methotrexate- induced chemobrain

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ABSTRACT

Chemobrain is a critical life-threatening condition that cancer patients can face during or after chemotherapy. It affects many aspects of the patient's cognitive ability and it appears as a defect in the cancer survivor's memory or concentration. The learning capacity, attention, and executive function can also be influenced. The majority of the time, it manifests subtly and causes momentary, short-term effects. However, a variety of chemotherapeutic drugs adversely affect the quality of life of patients. Continuous, long-term cognitive adverse effects in specific circumstances can emerge from the chemotherapy regimen whether prescribed as monotherapy or as an element in therapeutic plans. This review is deliberated to highlight the mechanisms behind the pathophysiology of chemobrain, with a concentration on the cytotoxic agent 'methotrexate'(MTX), which has been revealed to be involved in arduous neurotoxicity. MTX is considered a folate antagonist. It was initially employed for treating different cancer types as well as several anti-inflammatory and/ or immunological disorders. This review is deliberated to highlight the potential pathways responsible for MTX neurotoxicity. Furthermore, the evaluation of the cognitive impairment, detected either in human or in animal models after chemotherapy, is one of the main topics of interest adopted in this article. The likely pharmacotherapeutic interventions and different behavioral tests are also discussed.

Keywords: Chemobrain; Methotrexate; Chemotherapy; Cognition; Neuroprotection; Hippocampus.

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1. Chemobrain (chemotherapy-induced cognitive impairment)

Cytotoxic chemotherapy will remain a cornerstone in contemporary oncology treatments. As survivability rates expand, after-treatment well-being is of high concern. Chemotherapeutic drugs administered systematically can cause toxic consequences in healthy organs, leaving patients struggling with innumerable side effects [1]. Chemobrain or chemotherapy-induced cognitive impairment (CICI) can be defined as the presence of

cognitive decline linked to various anti-neoplastic agents, irrespective of the type or site of the tumor or whether or not metastasis to the brain is present. In 1980, it was the first time to detect chemobrain when patients having different types of cancers had noticeably low scores in evaluations testing different mental and cognitive abilities during or post chemotherapy [2]. Symptoms of CICI include memory problems, lag in processing speed, incapability to focus, and language disturbances [3]. Recently, there has been growing evidence that there is an elevated occurrence of cognitive dysfunction in cancer

survivors due to antineoplastic drugs given to treat different solid tumors, principally breast, lung, ovarian, and prostate malignancies [4]. Patients suffering from breast cancer who take auxiliary chemotherapy were reported to be one of the specially stated categories of patients facing a permanent decline in cognitive functions (decrease in comprehending new information and decreased recalling new information, decrease in cognitive control and response time). Consequently, it is not abnormal for patients to want to converse about "chemobrain" as a probable adverse effect of auxiliary chemotherapy and to consider it when deciding whether to take this potentially life-maintaining treatment or not [5]. CICI can be described as the deterioration of patients' capacity to acquire knowledge, concentrate, or make decisions. The majority of the time, it manifests subtly and causes momentary, short-term effects [5]. In contrast, a variety of chemotherapeutic drugs typically exert continuous, long-term cognitive side effects in specific circumstances whether given alone or as a part of the treatment regimen, further adversely influencing the quality of life (QOL) of patients suffering from solid tumor cancer [6].

2. Pathogenesis of Chemotherapy-Induced Cognitive Impairment

Its etiology is most likely complex, including interrelated mechanisms that affect patients' cognitive function and central nervous systems (CNS) directly or indirectly.

Lengthy cognitive impairment in cancer patients can be remarkably predicted and determined by genetic factors. It has been documented that in comparison with individuals with other APOE alleles, survivors from different cancer types possessing the allele e4 of apolipoprotein E (APOEe4) are at higher risk of developing more noticeable intellectual impairment [7]. Common chemotherapeutic

drugs are impotent to significantly pass the blood-brain barrier (BBB). The BBB's structure can be altered by genetic variation in its transporters, letting minute doses of chemotherapy pass to the neural tissues. Patients with genes linked to either less effective DNA repair pathways or genes for multidrug-resistance-1 (*MDR 1*) that codes for the protein P-glycoprotein, are thought to be the most susceptible to developing side effects of drugs that may include CICI [8]. It has been shown that even minimal quantities of chemotherapeutic agents are noxious to brain parts linked to cognition, involving the death of different cells and decreased cell multiplication [9]. The BBB can be penetrated by some commonly used conventional chemotherapies, such as methotrexate (MTX). By leading to harmful events to microglia, oligodendrocytes, and neuronal axons, after demyelination, variations in water content and levels of neurotransmitters, these antineoplastic agents can trigger a direct neurotoxic effect on the CNS, possibly causing cognitive dysfunction [10, 11]. Hormonal changes owing to chemotherapy-induced menopause can also have a negative impact on patients' cognitive function due to the decline in estrogen hormones which have neuroprotective effects. In addition, because of lower levels of testosterone and estrogen, people receiving hormonal therapy either male with prostate cancer or female with breast cancer, may suffer from cognitive impairment [7]. The importance of estrogens in maintaining telomere length, in antioxidative influence, and the protective effects on neurons are highlighted in several trials, which state that decreased levels of these hormones as a consequence of a hormonal treatment plan can cause chemobrain even when administered as mono-therapeutic regimen devoid of chemotherapy. From the side, oxidative stress can play a role in chemobrain. It can cause DNA damage that affects the CNS [7]. Oxidative

stress is a disturbed balance in the generation of reactive oxygen species, which comprises free radicals and peroxides. Particularly, exposure to exogenous toxins results in the production of free radicals. As an alternative, certain free radicals form naturally during endogenous metabolism to combat germs and viruses [12]. Chemotherapy can reduce antioxidant power and cause point mutations in the DNA of the mitochondria, thus causing cognitive impairment [7]. Cancer-related anemia (CRA) is another known side effect of cancer and/or chemotherapy. By lowering cerebral oxygenation, CRA has been related to a variety of devastating manifestations, including cognitive decline, decreased visual memory, and difficulties with executive function tasks. This has a profoundly negative impact on the quality of life for cancer patients [13, 14]. Lastly, immunological dysregulation evolving from chemotherapy or the cancer itself may play a role in the pathophysiology of CICI. This dysregulation may produce inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha that can pass the BBB [15].

3. Risk Factors Affecting CICI

A person who has survived cancer may also be more susceptible to developing CICI if they are older, have a history of head trauma, have other neurological conditions, have developmental abnormalities, or have micro metastasized brain tumors, especially if they have lung cancer. Demographic traits like intelligence quotient and educational attainment may potentially make a person more susceptible to CICI [16].

4. Physiological disturbances enhancing Chemotherapy-Induced Cognitive Impairment

In reaction to chemotherapy, some mechanisms are involved in the induced

cognitive decline as well as the neurotoxicity of the hippocampus. From these mechanisms, BBB disturbance, high levels of reactive oxygen species, and mitochondrial defects can be stated. In addition, increment of pro-inflammatory cytokines, reduction in anti-inflammatory cytokines, and impaired integrity of white matter are from the detected pathways [17]. The hippocampus is particularly vulnerable to injury caused by systemic injection of several chemotherapeutic drugs, either directly or indirectly. Following chemotherapy, decreased hippocampal volumes can be linked to many pathologic alterations. Notably, in response to various kinds of chemotherapeutic medications, abnormalities in neural architecture, involving decreased branching of the dendrites and the spine density, have been seen in the hippocampus, implicating the dentate gyrus. The neuronal mechanism most commonly studied to be impacted by chemotherapy is hippocampal neurogenesis [18].

5. Methotrexate

5.1. Overview

MTX is an anti-metabolite that was initially introduced for treating different types of malignancies [19] and is additionally employed in non-malignant diseases like inflammatory or immunity-related problems. It is nowadays employed for treating resistant rheumatoid arthritis [20]. MTX stands as the most studied drug linked with chemobrain and neurotoxicity. It acts as a folate analog, blocking DNA replication by inhibiting purine and pyrimidine synthesis [21]. Pharmacological therapies have been observed to have a relatively responsive effect on the neurotoxicity and cognitive impairment induced by MTX. Many side effects can cause cancer patients receiving MTX such as nausea, fever, fatigue, and cirrhosis. In addition, increased risk of infection, GI bleeding, pancreatitis, and alopecia are often seen with

MTX administration. Unfortunately, aplastic anemia, teratogenesis, interstitial pneumonitis, and renal impairment can present also a great risk for those patients.

5.2. Intracellular metabolism of MTX

5.2.1. Polyglutamatation of MTX

According to several studies in tumor cell lines [22], MTX binds to two to five polyglutamate groups to be converted to polyglutamate forms. Due to this polyglutamylolation, MTX does not pass across the cell membrane in considerable amounts which expands its intracellular half-life [23]. The chain length of the polyglutamate straightaway controls the holding of its forms. High amounts of unbound MTX-Glu4 and nearly all MTX-Glu5 stay not less than 24 h after the elimination of the drug in the extracellular domain, when in fact an outstanding portion of MTX-Glu2 and MTX-Glu3 is discarded from the cell [23]. The development of the polyglutamate forms of MTX contributes to its cytotoxic and selective power. The inhibition of dihydrofolate reductase is not the only characteristic feature of those polyglutamated derivatives. They possess an increased affinity for some enzymes which are folate-dependent like thymidylate synthase, 5-amino-imidazole-4-carboxamide ribonucleotide transformylase, and the triple complex of enzymes that interconvert various forms of reduced folates [24]. Using ATP as its energy source, the enzyme folypolyglutamyl synthetase, which takes charge of MTX conversion, catalyzes the introduction of glutamate in gamma linkage to the end carboxyl group of the neighboring folyl glutamate. The enzyme's activity, initially detected in red blood cells and later in the human hepatocytes, was found to change among cancer cell lines. It was hypothesized that compromised polyglutamation is considered a mechanism of cancer refractoriness to MTX, together with

dihydrofolate reductase enzyme (DHFR) gene duplication [23].

5.2.2. Hydroxy-methotrexate (7-OH-MTX)

It involves the hydroxylation of MTX by hepatic aldehyde oxidase at the pterine ring, especially at the 7-position of this ring to form 7-OH-MTX. This reaction serves as a major detoxification pathway [26].

5.2.3. Diamino-2,4-N-10-methylptericoic acid (DAMPA)

In a living context, a carboxypeptidase of the gut bacterial normal flora rapidly converts MTX to DAMPA. About 5% of the intraperitoneally injected MTX in mice is converted to DAMPA through metabolism. Since MTX is a more powerful DHFR inhibitor than the latter and its hydroxy-modified version, 7-OH-DAMPA, it is feasible that this conversion represents xenobiotic detoxification [27].

5.3. Methotrexate neurotoxicity

One of the negative effects of using MTX is neurotoxicity, which varies depending on the dosage, method, and frequency of administration. High dosage, intrathecal injection, and young age all raise the likelihood of occurrence. Although the likely multi-factorial processes for neurotoxicity aren't completely understood yet, they are believed to exist [27]. The literature suggests that there may be a direct neuronal injury or a change in the folate homeostasis in the CNS. The following circumstance occurs: Homocysteine amounts in the blood rise as a result of MTX's suppression of the hydro folate reductase, which influences the homocysteine quantities. In such a manner, not only does this substance arouse a direct effect of toxicity for the endothelium, but also its metabolism will act as an agonist of the NMDA receptor, likely emerging from this condition the neurological findings related to the neurotoxicity [27].

Additionally, the release of adenosine from the fibroblast and the endothelium is a possible neurological lesion. Nowadays, it is documented that there is a genetic variation related to neurogenesis that could lead to the neurotoxicity sensibility induced by MTX. Trimethoprim/sulfamethoxazole, acetylsalicylic acid, nitric oxide, non-steroidal anti-inflammatory drugs, penicillin, and proton pump inhibitors can delay MTX clearance and increase the risk of its neurotoxicity; therefore, they must be evaded before and after the introduction of high doses of MTX [28].

5.4. Clinical Symptoms of MTX neurotoxicity

5.4.1. Acute Neurotoxicity

It appears shortly after high-dose (61 g/m²) MTX infusion, drowsiness, confusion, tiredness, and seizures may develop [29]. Acute(chemical)arachnoiditis may be associated with intrathecal MTX. This condition happens in 5-40% of patients, commonly 2-4 h after the dose administration, and persists for a maximum of 72 h. The most usual manifestations of arachnoiditis manifest as headache, GIT disturbances, back pain, elevated temperature, and vertigo [29]. The acute neurotoxicity is most probably linked to the administered dose and the culminating MTX levels in the cerebrospinal fluid.

5.4.2. Subacute Neurotoxicity

An encephalopathy that includes hemiparesis, ataxia, speech impairment, seizures, disorientation, and emotional abnormalities may develop days to weeks after exposure to MTX [30]. 'Stroke-like syndrome' is the term used to describe these symptoms. Following 48-72 h, patients typically recover spontaneously, and additional MTX treatments do not enhance the chance of this syndrome recurring. Significant myelopathy may result from intrathecal MTX, which may then cause symptoms such as leg discomfort, sensory abnormalities, paraplegia,

and bladder control problems. No obvious vascular abnormalities or inflammation are found in pathologic studies. Highly intensive short-treatment sequences or long-term progressive treatment are regarded as endangering parts for subacute toxicity [31].

5.4.3. Chronic Neurotoxicity

After MTX therapy, this type of neurotoxicity may emerge months or years later. Leukoencephalopathy is the most significant syndrome in this phase. It presents with a myriad of symptoms such as confusion, drowsiness, or anger. Additionally, dementia, and disturbance in speech or vision may also appear. In more drastic conditions, quadriplegia or coma may take place. Unfortunately, death can also be a consequence of this neurotoxicity [34]. In contrast, partial recuperation or stabilization is probable, mainly in younger age [35]. Leukoencephalopathy mainly involves the white matter [36], particularly the periventricular areas and the centrum semi-oval. Demyelination happens in this phase as well as necrosis of the white matter, astrocytosis, and axonal defect [34]. Intracerebral calcifications and mineralizing microangiopathy have been identified. Cellular events comprising inflammation have not been detected [32-34].

5.5. Resistance to MTX

The emergence of resistance against MTX abides as one of the main barriers to the extent of clinical effectiveness of this molecule. It can happen due to various mechanisms, involving expression of *mdr1*, altered transport, variation of the target enzyme DHFR so that the affinity for MTX is declined [38], overproduction of DHFR, and lower cellular ability to convert MTX to polyglutamate [22].

5.6. Effects of MTX on different pathways

5.6.1. Effect of MTX on apoptosis

Apoptosis is a regulated way of cell death, which is essential in maintaining tissue homeostasis, additionally, it represents a technique by which destroyed, infected, or neoplastic cells are constantly removed without the induction of inflammation [39]. Indeed, one of the principal inducers of apoptosis is the disturbance in the oxidative state [40]. Not only can oxidative stress, caused by various stimuli, provoke apoptosis [41], but also antioxidants can protect the cell against apoptosis even when it is induced by stimuli that don't cause a direct oxidative effect [42]. Apoptosis constitutes a regulated form of cell death. It begins with certain unique signals and is affected by genes responsible for both cellular survival and death. Hamster ovarian cells were the first targets where MTX-induced apoptosis was studied [43]. MTX was reported to exert its anti-inflammatory effect by enhancing apoptosis in inflammatory cells like lymphocytes. It was also detected in a recent study [44] that the inhibition of the conversion of BH₂ dihydrobiopterin (BH₂) to tetrahydro pterin (BH₄) is mediated by MTX which stops the action of the DHFR enzyme. The decrease in BH₄ leads to a change in the cellular response to apoptosis. Consequently, a deep need for focusing on the effect of MTX on reducing the reduction of BH₂ to BH₄ has recently emerged. The death receptor and different pathways involving the mitochondria are the main ways by which MTX elevates the cellular sensitivity towards apoptosis. High apoptotic sensitivity depends on the elevated expression of Jun-N-terminal kinase (JNK) and its target genes. JNK stimulation is regulated by ROS, which we suggest is triggered by MTX-dependent exhaustion of BH₄ levels, separating eNOS from NO formation, and leading to the excessive presence of ROS. Apoptosis could begin either through the intrinsic pathway, cell kills itself by reacting to the intrinsic stress, or through the extrinsic pathway, cell kills itself relying on

signals from different cells. The cooperation between Bax as a pro-apoptotic protein and Bcl-2 as an anti-apoptotic protein can control the susceptibility of cells to apoptosis [45]. Therefore, MTX mediated an apoptotic effect via increased Bax and declined Bcl-2 levels showing the variation in the pro-apoptotic/anti-apoptotic markers quantification. Also, the immunohistochemical intensity signal of caspase 3 was increased indicating the apoptotic effect of MTX.

5.6.2. Effect of MTX on autophagy

The goal of autophagy is to destroy and repair destroyed organelles and improperly folded proteins by directing them to the autophagosome-lysosome system. Autophagy is a cytoprotective means that protects the cell against death. As a result, increased levels of reactive oxygen species (ROS), malfunctioning mitochondria, and oxidative stress have all been linked to defective autophagy [46, 47]. Macroautophagy represents the most common form of autophagic processes. In a previously implemented study on spermatogenesis, MTX was found to enhance autophagy which indicates that autophagy contributes to the impairment in spermatogenesis induced by MTX [48]. Furthermore, MTX was documented to provoke inadequate autophagy as detected by decreased levels of Beclin 1 and augmentation of p62 SQSTM1 protein [49]. The increment in p62 SQSTM1 is proof of defective autophagosome destruction and malfunctioning autophagy pathway [50].

5.6.3. Neurogenic Depletion and Memory Dysfunction Using MTX

The gradual loss or destruction of neural cells is one of the bad outcomes of some neurotoxic substances such as MTX. In an earlier study [51], Ki-67-positive cells were significantly suppressed after the administration of MTX in

experimental rats. Those experimental models performed normally in the Morris water maze test, after being injected with a high concentration of MTX. In contrast, after the removal of the platform on the test day, the MTX group showed decreased investigation of the place where the platform was previously located. Moreover, they showed a declined behavior on a novel object recognition task. These findings revealed a deterioration of anterograde memory [51]. In an investigational study, the study of the effect of MTX on retrograde memory was an important scope. Rats were exposed to different behavioral tests like context fear conditioning task to assess their memory before and after MTX [52]. Morris water maze was also a test of interest. Another study performed by Sritawan and some of his research partners assessed the disturbances created in the hippocampus and the neurogenic defects that appeared after MTX treatment. This experimental design was conducted over a period of two weeks. The results of affected memory became clear after approximately 6 days after the injection of MTX. A deterioration in behavior in novel location memory was detected [53].

5.6.4. MTX and its relation to inflammation

MTX and MTX polyglutamate molecules are capable of inhibiting 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase. This enzyme represents one of the enzymes involved in folate synthesis and is consequently related to purine synthesis [55].

This enzyme takes charge of the conversion of AICAR into formyl-AICAR. This formed molecule acts as a precursor for DNA purines. As a result, when the function of transformylase is absent, its product will decline in amount and its substrate, AICAR, will build up within the cellular compartment. High amounts of AICAR will lead to the stoppage of adenosine deaminase enzyme action. Therefore, adenosine molecules

will accumulate in the extracellular field. Indeed, adenosine has a crucial role in the anti-inflammatory response of MTX. This effect happens from the interaction of adenosine with some cell surface receptors, leading to an effective inhibition of chemotaxis of leukocytes. Additionally, the oxidative inflammation taking place in either neutrophils or monocytes will be also inhibited. On another side, the synthesis of cytokines such as IL-6, IL-12, and TNF-alpha will be hindered [54].

5.6.5. Effect of MTX on oxidative stress

Earlier studies have documented that MTX leads to elevation in ROS, which stops the cell cycle and leads to cell death in the CNS through the p53/p21 activation [55, 56]. In fact, due to the elevated metabolic rate of the brain and the extensive amount of polyunsaturated fatty acids, the brain is a very sensitive organ to the disturbance in the oxidative state. Also, it has a low antioxidant power which increases its risk of facing oxidative stress. Indeed, decreasing reactive oxygen species and targeting oxidative stress can preserve readily against the neurological toxicity of MTX. MTX administration has been linked to harmful effects in various organs such as the brain, spinal cord, intestine, and liver [56]. It causes an increase in ROS production as well as a decrease in antioxidant defensive mechanisms in the affected tissues. Malondialdehyde (MDA), which results from lipid peroxidation, increases in amount by MTX. Furthermore, glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) declined levels are all proofs that MTX-induced oxidative stress. Since Nrf2 is essential for the expression of antioxidant genes like HO-1, CAT, and SOD, it implies that Nrf2/HO-1 pathway activation was linked to antioxidant consequences and this pathway is readily influenced by MTX injection. This pathway can also lower the expression of iNOS and NF- κ B in

tested animal models [57].

5.6.6. Effect of MTX on Neurotransmitter levels

Fundamentally, the hippocampus represents the principal part of the limbic system being included in different learning activities and memory executive functions [58]. Hippocampal monoamines have been implicated in different behavioral patterns, including learning and memory. Therefore, the assessment of amines present in the hippocampal tissues after the administration of MTX could be suggested to unveil insight into the probable pathways involved in neurotoxic events. Extensive work has been done to decode the interconnection between hippocampus brain amine levels and learning and memory function. Behavioral examinations have proposed that brain amines, primarily norepinephrine, serotonin, and dopamine, play some essential role in memory processing [59]. Learning and memory functions were varyingly impacted by altered amounts of brain amines. Norepinephrine injections into the entorhinal cortex and CA1 region of the hippocampus improved both short- and long-term memory [60]. Therefore, it is obvious that norepinephrine facilitates memory and learning. The brainstem's locus coeruleus is a preliminary origin of information for the hippocampus and it is highly affected by norepinephrine amounts. Moreover, Dopamine is one of the considered amines in learning and memory processes. The receptors of Dopamine were detected to play a role in memory either at the cortical or at the hippocampal level [61]. Dopamine receptor agonists administration to the cortex enriched spatial memory. Accordingly, hippocampal dopamine seems to have a boosting role in memory processing. Dopamine levels declined significantly in the hippocampus due to MTX [62]. Taken together, it seems that an impaired dopaminergic system is related to cognitive

dysfunction triggered by MTX.

6. Impact of chemobrain on subjects' life

Along with illness and mortality, health-related quality of life (HRQOL) is acknowledged as a significant health outcome in the context of public health [63].

A greater appreciation for both length of life and quality of life can be seen in HRQOL. Physical health, mental health, social health, and role functioning are all parts of HRQOL.

6.1. Many predisposing factors may contribute to chemobrain development including: [64]

Females exhibit higher vulnerability in comparison with males, age (60±5 y), education, and IQ. In addition, dietary factors are associated with increasing risk for chemobrain such as vitamin D deficiency. On the other hand, immune response, anemia, hormonal levels, anxiety, and depression were also detected. When they begin to reinitiate their careers, especially for those in mentally processing jobs, several patients who have survived breast cancer have grumbled of decreased reaction speeds and problems multitasking, which become more dominant. According to Wagner et al. [65], 63% of survivors showed difficulties in paying attention and focusing, 50% reported memory defects, and 38% were familiar with issues with abstract reasoning.

7. Assessment of cognitive dysfunction

7.1. Assessment of cognitive dysfunction in humans

7.1.1. Magnetic resonance imaging (MRI)

To evaluate cognitive dysfunction as well as highlight the plausible pathways responsible for chemobrain, MRI serves as a powerful diagnostic tool. Studies revealed a continuous decrease in neuropsychological processes approximately after 5 years of chemotherapeutic plan

finalization. Furthermore, an empirical investigation implemented on some patients who have survived breast cancer 3 to 10 years after their anti-neoplastic regimen, linked the increased oxidative DNA damage and the decreased grey matter density as well as lower functional MRI activation in specific brain regions [66].

7.1.2. Neuropsychological tests

The International Cognition and Cancer Task Force (ICCTF) affirmed that the testing of neurological performance represents the core for evaluating cognitive functions even though MRI is very significant in evaluating CICI. The following tests have been specifically suggested in this regard: The Controlled Oral Word Association test, the Trail Making Tests A and B, and the Hopkins Verbal Learning Test which has been revised. Subjective patient reports are excellent in clinical settings and more presumably to reveal the patients' reduced QOL than objective evaluations that might not shield all of the patients' influenced regions, even though the ICCTF does not view them as a definitive method in evaluating chemobrain [67, 68].

7.1.3. Electroencephalography (EEG)

By using electrodes to assess various brain activities after chemotherapeutic intervention, EEG seems to be a beneficial method. Furthermore, it is non-invasive letting the patient feel safer.

Many researchers stated that the neurological stimulation and latency in different cancer survivors were easily detected by EEG after 5 years of chemotherapy. Despite the power of this technique, other studies documented no noticeable variations in EEG results between untreated healthy persons and cancer cases who were in continuous use of chemotherapy [69].

7.1.4. Positron emission tomography (PET)

For several cancer patients, PET is considered a useful research and diagnostic tool. For imaging, it employs the radiopharmaceutical 18-fluorodeoxyglucose (FDG). This compound was employed to investigate the cellular metabolic processes and to identify, treat, and diagnose various CNS disorders, such as Parkinson's, depression, and Alzheimer's. In experimental animals, chemotherapy was found to decline the metabolism of glucose molecules in both the hippocampal and cortical tissues which causes later mental decline in those subjects [70]. PET scans were used to assess variations in the metabolism of different cerebral patterns in assessing the link between the treatment with aromatase inhibitors and intellectual damage [71]. Additionally, using PET analysis following concurrent chemotherapy for breast cancer, a relationship between pro-inflammatory cytokines, localized cerebral metabolism, and mental complaints was detected.

7.2. Assessment of cognitive decline in experimental animal models

Because experimental animal models allow the simulation of human diseases, the explanation of underlying mechanisms, and the development of satisfactory therapeutic plans that cannot be directly tested in human beings, animal models are considered a fundamental component of clinical research.

7.2.1. Passive avoidance

The Passive Avoidance test represents a fear-exasperated test employed to assess learning and memory in rodent experimental models of CNS diseases. In this test, animals acquire the knowledge of avoiding a surrounding in which a noxious stimulus (such as a foot shock) was formerly applied. The Passive Avoidance task is beneficial for assessing the impact of new chemical substances on learning and memory besides exploring the mechanisms included in

cognition [72]. The administration of MTX systematically has been documented to hinder annoyingly stimulated memory in different subjects [73].

7.2.2. Morris Water Maze

In this test, experimental animal models must learn to swim in a wide circular black pool of water that has been surrounded by external cues. The primary variables that are measured are escape latency, the number of crossings that occur at that precise location, the amount of time consumed in the quadrant of interest relative to the opposing quadrant, swimming speed, and swimming path length. The animals treated with MTX manifested a longer latency time to cross the platform location in the probe trial, showing a defect in spatial memory function. There was additionally a tendency for these animals to spend less time in the right quadrant in comparison with the control animals [51].

7.2.3. The Novel Object Recognition Test (NORT)

Is considered a behavioral experiment that is usually used to examine different facets of learning and memory in mice. Three days can be dedicated to the relatively easy-to-understand ORT: the testing, training, and habituation days. The mouse is permitted to investigate two identical objects throughout training. One of the practice items gets swapped out for a new one on test day. Given their natural predilection for novelty, mice will gravitate towards the novel object if they recognize the familiar one [73]. The rats given MTX in the NOR test were unable to discriminate between a new and a known object, suggesting a decline in the hippocampal comparator function [74].

7.2.4. Y-maze

To test laboratory mice's spatial working memory, the Y-maze test is frequently used. The

test is based on rodents' inclination to explore novel settings naturally. Animals will first study a different arm of a maze before going back to the one they previously explored since rodents normally prefer to investigate unfamiliar situations rather than familiar ones. This task involves a variety of brain parts, encompassing the hippocampus, septum, basal forebrain, and prefrontal cortex [76]. The decline of memory confirmed by the behavioral tests in which MTX was administered was documented [73].

8. Coping with chemobrain

8.1. Non-pharmacological strategies

8.1.1. Social Support

During cancer therapy, social support is crucial in helping patients manage their symptoms. Social connections or medical specialists who provide patients with emotional and supportive counseling are two possible sources of this support. Patients can benefit from this support, especially when it comes from people closest to them. Family members, for instance, are frequently a tremendous source of support for cancer patients and have been shown to ameliorate QOL and lessen symptom severity. Additionally, it has been discovered that patients who depend more on their friends for emotional and social support adjust psychologically better both during and after receiving a cancer diagnosis. This is probably because when someone feels vulnerable, they are more inclined to ask for social and emotional support. Social support can also assist patients in coping with their disease's physical side effects. For instance, by exchanging experiences and learning about other people's symptom-management strategies, support groups might help patients control their nausea and exhaustion [77].

8.1.2. Cognitive-Behavioral-Therapy (CBT)

CBT is a psychosocial talking type of therapy

that addresses intellectual health issues by creating individual management plans to address current issues and modify negative thoughts, behavior, and emotional patterns, thereby reducing psychological and emotional disturbances [78]. Three studies, found in the literature added appropriate CBT methods to aid in chemobrain improvement. The first one used memory and attention adaptation training (MAAT) as an intervention. It was a single-arm pilot study. The participants reported improvements in their self-assessment of improved QOL and altered mental function.

Furthermore, patients improved on post-treatment neuropsychological tests as well as at the follow-ups that took place in the second and sixth months, respectively. The second experiment was a randomized clinical trial (RCT) with two groups: MAAT and no treatment control. The survivors of breast cancer going through MAAT were evaluated at the beginning and after 8 weeks of treatment. MAAT contributors achieved remarkable progressions in comparison with the baseline group on verbal memory and the spiritual well-being subscale of the Quality of Life-Cancer Survivors scale. However, the self-report of daily cognitive defects did not reach statistical significance. The third study used a secondary investigation of data from an RCT to assess whether patients would report less cognitive decline following CBT treatment for cancer-related fatigue. Patients with cancer who experienced extreme fatigue underwent a 6-month cognitive behavioral therapy intervention that focused on identifying the underlying causes of their fatigue. Participants in CBT consequently reported noticeably less cognitive dysfunction [79].

8.1.3. Physical activity (exercise)

Resistance training associated with physical activity has been found to improve cognitive functions by upregulating the gene expression of

brain neuroprotective agents.

Furthermore, physical activity has a major positive effect on hippocampal neurogenesis [80]. An animal model of chemobrain revealed that post-treatment activity suppressed chemotherapy-enhanced suppression of neuron formation and ameliorated cognitive levels [81].

8.2. Coping by drugs

8.2.1. Symptomatic Treatment Approaches

8.2.1.1. Methylphenidate

Methylphenidate is a medication used for narcolepsy and attention-deficit/hyperactivity disorder. In light of methylphenidate being employed prosperously to handle cognitive deterioration in patients with brain tumors and in children having cancer [16], its potential for helping survivors with solid tumors who are experiencing cognitive decline is found to be highly promising. Taking into consideration the probable link between cognitive dysfunction induced by chemotherapy and unbalanced catecholamine levels, drugs that raise catecholaminergic tone may contribute to alleviating the resulting cognitive issues.

Methylphenidate is a dopaminergic and noradrenergic agonist. It inhibits monoamine oxidase enzyme activity and reduces dopamine uptake at synapses. It has received extensive evaluation in the context of cognitive impairment brought on by chemotherapy. The impact of methylphenidate on cognition and lethargy was examined in patients who had undergone breast cancer resection. Those patients were receiving chemotherapy in a randomized, placebo-controlled, double-blinded experiment. Regrettably, there was no statistically remarkable difference between the methyl-phenidate-treated group and the placebo group [82].

8.2.1.2. Psychostimulants

They have already been used to treat fatigue

brought on by cancer and cognitive impairment linked to cancers.

An FDA-approved stimulant called modafinil is used to treat narcolepsy and improve wakefulness. As a follow-up to a trial to determine whether modafinil is effective at reducing cancer-related fatigue, it was previously studied to see how it affects cognitive decline in breast cancer survivors [83]. It was discovered that Modafinil remarkably ameliorated episodic memory and memory performance rate when compared to the placebo group [83]. To assess Modafinil's impact on cancer-linked fatigue and mental dysfunction, a pilot study was done. Unexpectedly, modafinil ameliorated the QOL and reduced fatigue, but no noticeable cognitive change was found [84].

8.2.1.3. Fluoxetine

One of the selective serotonin reuptake inhibitors used primarily to treat depression is fluoxetine. Previous research demonstrated that Fluoxetine enhances the level of brain-derived neurotrophic factor and promotes hippocampal neurogenesis, two potential mechanisms contributing to the pathogenesis of cognitive decline emerging after chemotherapy. As indicated by the animals' ameliorated performance on new recognition, fluoxetine reversed chemotherapy-induced cognitive deterioration [85].

8.2.2. Neuroprotective Treatment Approaches

8.2.2.1. Ginkgo Biloba

Ginkgo biloba is a known herbal compound employed usually for protecting against intellectual deterioration in old patients [86]. It has been proven that its administration is efficacious against chemobrain. Ginkgo biloba was detected to possess antioxidant power and neuroprotective characteristics which may contribute to its maintenance of cognitive

function [87].

8.2.2.2. Donepezil

Donepezil, which is an acetylcholinesterase inhibitor, is presently described for some early stages of dementia, and it may also be efficacious for more severe phases [88]. In Alzheimer's disease, Donepezil is usually used as an effective way of treatment. Given that chemotherapy-induced cognitive dysfunction may be caused by hippocampal-dependent memory loss, donepezil may improve mental function in these cases. A clinical trial with randomization, double blinding, and placebo control was performed on patients who had survived breast cancer and who had concomitant chemotherapy one year prior and were undergoing CICI treatment. The donepezil-administered group showed noticeably better verbal memory; in contrast, no noticeable difference in other cognitive or subjective measures was documented [89].

8.2.2.3. Antioxidants

Earlier gathered data in the noncancer condition reveal that vitamin E with high dosage is capable of preventing or improving mental deterioration by hunting free radicals [90]. Considering that systemic cytotoxic drugs for cancer are capable of producing ROS and also intercede with the acetylcholine-involved pathways of the brain, thus causing CICI, one could propose that vitamin E also may be efficacious in preserving the cognition of cancer survivors.

Conclusion

There is strong evidence from clinical research and animal models that chemotherapy causes cognitive impairments. Oxidative stress, neuroinflammation, disturbance of apoptotic and autophagic pathways, manipulation of principal kinase enzymes, reduction in the level of neurotransmitters, as well as genetic and

epigenetic factors, are some of the potential pathways behind chemobrain. In addition, the hippocampal neurogenesis represents a target that, when affected, leads to an increase in chemobrain development risk. While behavioral reclamation improves the post-chemotherapy life for survivors of chemotherapy-induced cognitive problems, there is generally no proven solution for these issues. Additionally, several pharmacological drugs have been successful in demonstrating a potential effect in blocking neurotoxic pathways; nevertheless, it is still necessary to assess their influence on the anticancer efficacy of chemotherapy treatment plans.

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing interests

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