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Diagnostic and Treatment Approaches to Chemo Brain

Kemobeyin Tanı ve Tedavi Yaklaşımları

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ABSTRACT

Advancements in cancer treatment and the consequent increase in post-treatment survival have brought the challenges associated with cancer therapy into sharper focus. Many treatment modalities, such as chemotherapy, are administered systemically, leading to significant systemic side effects. Cognitive impairments, including deficits in executive functions, attention, memory, word finding difficulties, and the inability to acquire new skills, can arise during and after cancer treatment, a phenomenon known as "chemo brain." Post-chemotherapy cognitive impairment can be observed at high rates and may persist long-term in nearly one-third of cases, resulting in a decline in quality of life and functional impairment. Proposed mechanisms underlying the pathophysiology of chemo brain include disruption of blood-brain barrier integrity leading to increased permeability and brain susceptibility, DNA damage and associated deficiencies in DNA repair, telomere shortening, oxidative stress, pro-inflammatory cytokines and neuroinflammation-neurotoxicity, neuronal genetic susceptibility and epigenetic changes, post-chemotherapy hormonal alterations, reactive oxygen radicals and effects, loss of spinal and dendritic arborization, microtubule disintegration, reduced neurogenesis, neurotransmitter alterations, mitochondrial dysfunction, and loss of spinal density. This review aims to evaluate the characteristics, clinical manifestations, pathophysiology, and options for prevention or treatment of chemo brain, accompanied by current literature findings, thereby contributing to the existing body of knowledge.
Keywords: Cancer, chemotherapy, chemo brain, blood-brain barrier, cognitive loss

ÖZ

Gelişen kanser tedavileri ve artan tedavi sonrası yaşam süreleriyle birlikte, kanser tedavisinin yol açtığı sorunlar daha belirgin hale gelmiştir. Kemoterapi gibi birçok tedavi, sistemik olarak uygulanmakta olup bu da ciddi sistemik yan etkilere neden olmaktadır. Kanser tedavisi sürecinde ve sonrasında, bilişsel kayıplar ortaya çıkabilir. Bu kayıplar, yürütücü işlevlerde bozulma, dikkat ve hafıza sorunları, kelime bulma güçlüğü ve yeni beceriler edinememe gibi belirtilerle kendini gösterebilir. Bu durum, "kemobeyin" olarak adlandırılmaktadır. Kemoterapi sonrası bilişsel bozulma yüksek oranlarda gözlemlenebilir ve bazı durumlarda uzun süreli olabilir. Bu da yaşam kalitesinde düşüşe ve işlevsellik kaybına neden olabilir. Kemobeyin patofizyolojisi üzerine öne sürülen mekanizmalar arasında, kan-beyin bariyeri bütünlüğünün bozulmasıyla geçirgenliğin ve beyin hassasiyetinin artması, deoksiriboz nükleik asit (DNA) hasarı ve buna bağlı DNA onarımı eksiklikleri, telomer kısalması, oksidatif stres, proinflamatuar sitokinler ve nöroinflamasyon-nörotoksisite, nöronal genetik yatkınlık ve epigenetik değişiklikler, kemoterapi sonrası hormonal değişiklikler, reaktif oksijen radikalleri ve etkileri, spinal ve dentritik arborizasyon kaybı, mikrotübül disentegrasyonu, azalmış nörogenesis, nörotransmitter değişiklikleri, mitokondrial disfonksiyon ve spinal dansite kaybı yer almaktadır. Bu derleme, güncel literatür bilgileri eşliğinde kemobeyin özellikleri, klinik belirtileri, patofizyolojisi ve kemobeyini önlemeye ya da tedavisine yönelik seçeneklerin değerlendirilmesini amaçlamaktadır.
Anahtar sözcükler: Kanser, kemoterapi, kemobeyin, kan-beyin bariyeri, bilişsel kayıp

Introduction

Cancer is a disease that is increasingly prevalent worldwide, can be observed at almost any age, and leads to significant morbidity and mortality. Despite advances in treatment, some types still have a low chance of a cure and can recur (Piña-Sánchez et al. 2021). Cancer arises through errors in repairing deoxyribonucleic acid (DNA) damage, allowing abnormal cells that should typically die to survive and proliferate uncontrollably. It can originate from almost any part of the body and spread to adjacent tissues and organs. Additionally, cancer can

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metastasize, migrating to other parts of the body through various pathways such as blood vessels, lymphatic systems, and cerebrospinal fluid (Piña-Sánchez et al. 2021). Cancer is the leading cause of death worldwide, accounting for approximately 10 million deaths in 2020, which is nearly one in six deaths. In the United States, it is projected that 2 million new cancer cases and 611,720 cancer-related deaths will occur in 2024 (Dizon and Kamal 2024). There are numerous types of cancer, with the most common worldwide being breast cancer in women and lung cancer in men. In 2020, lung cancer ranked first as the leading cause of cancer-related deaths (Piña-Sánchez et al. 2021).

Smoking, ultraviolet radiation, ionizing radiation, arsenic, asbestos, aflatoxins, various viruses, and many other factors can contribute to the development of cancer. As age increases, the body's ability to eliminate damaged cells declines, and the likelihood of cancer development rises. Given that life expectancy is increasing worldwide and the elderly population is growing, it is a reality that cancer cases will dramatically rise. Cancer is named according to the tissue from which it originates and manifests through abnormalities in the functions of the affected tissues and organs, as well as general physical symptoms. As it continues to grow, the problems intensify, with metastasis introducing new losses and complications. Therefore, cancer prevention and early detection are of great importance (Piña-Sánchez et al. 2021).

Research on cancer treatment continues, and a wide variety of treatment options are available. These include surgery, chemotherapy, radiotherapy, bone marrow transplantation, stem cell therapy, immunotherapy, hormone therapy, and targeted therapy. The appropriate method is determined based on the type of cancer and its stage of progression. In some types of cancer, several treatment options may be applied together or sequentially. Most treatments, including traditional chemotherapeutic agents and newer therapies such as immunotherapy or targeted therapy, are associated with serious, sometimes long-lasting or irreversible side effects. The most well-known side effects of cancer treatment include hair and eyelash loss, appetite and weight loss, nausea and vomiting, reproductive function impairments, immune suppression, susceptibility to infections, and the development of severe infections even from simple pathogens. These treatment options can also have negative effects on the brain (Piña-Sánchez et al. 2021, Rao et al. 2022, Dizon and Kamal 2024).

As treatment options increase and life expectancy extends, the long-term side effects of cancer treatment are becoming more significant. Therefore, in addition to the known side effects of cancer treatment, the long-term neurocognitive effects are also becoming a subject of investigation. The concept of "chemo brain" is relatively new but is increasingly being researched in the literature. In this article, we aim to provide an overview of the concept of chemo brain and offer a perspective on approaches to diagnosis and treatment.

Description of Chemo Brain

Chemo brain is a term used to describe the thinking and memory problems that may occur during and after cancer treatment. It is also referred to as "chemo fog" or "chemotherapy-induced cognitive impairment" (CICI). Chemotherapy, in particular, can damage many types of body cells. When brain cells are affected or cognitive decline occurs due to chemotherapy-induced brain cell damage, it is referred to as chemo brain. In fact, chemotherapy-related brain damage was first noticed in 1980 and has since been supported by an increasing number of studies (Piña-Sánchez et al. 2021). The term "chemo brain" or chemotherapy-induced brain damage was formally introduced in 2002 (Ahles and Saykin 2002).

Chemo brain is associated with impairments in learning, memory, attention, and executive functions. Its prevalence varies between 17% and 76%, with 17% to 35% of these cases experiencing long-term effects that can last for over 10 years (Ahles and Saykin 2002, Wefel and Schagen 2012, Nguyen and Ehrlich 2020). This chronic cognitive decline can lead to decreased functionality and quality of life, making it difficult to tolerate. The wide range of findings across studies may be attributed to differences in methodology, the absence of a standardized tool to assess chemo brain, and a lack of correlation between clinical presentations of cognitive decline and the evaluation scales used.

Cancer diagnosis creates a serious psychological burden. In addition, cancer itself can affect the cognitive process with loss of ability and functionality, and these losses can become even more pronounced, especially in the presence of a brain tumor or metastasis to the brain. However, even when the effects of these factors are excluded, there is evidence supporting that chemotherapy can lead to cognitive decline (Nguyen and Ehrlich 2020, Rao et al. 2022).

To diagnose chemo brain, the essential criteria include a history of cancer diagnosis, undergoing cancer treatment, and the presence of cognitive decline during this process. While anxiety and depression caused by

the cancer diagnosis, as well as side effects like cachexia, anemia, pain, and sleep disturbances from the cancer or its treatment, can influence or exacerbate cognitive loss, they are not considered essential for a chemo brain diagnosis. Factors such as the type and location of cancer, treatment methods and chemotherapeutic agents used, age, other physical illnesses, and medications can also impact the development of chemo brain. Risk factors for chemo brain include having a brain tumor or cancer that has metastasized to the brain, receiving higher doses of chemotherapy or radiotherapy, direct radiotherapy to the brain, being at a young age, and increasing age in general.

Although the exact mechanisms behind chemo brain are not yet fully understood, several pathways have been proposed. These include disruptions in the blood-brain barrier (BBB) caused by chemotherapy, increasing permeability and brain sensitivity; DNA damage and related repair deficiencies; telomere shortening; oxidative stress; proinflammatory cytokines; neuroinflammation and neurotoxicity; neuronal genetic predisposition and epigenetic changes; hormonal changes post-chemotherapy; reactive oxygen species and their effects; spinal and dendritic arborization loss; microtubule disintegration; reduced neurogenesis; neurotransmitter changes; mitochondrial dysfunction; and spinal density loss (Nguyen and Ehrlich 2020, Rao et al. 2022).

Pathophysiology of Chemo Brain

Blood-Brain Barrier (BBB) Damage

The blood-brain barrier (BBB) is a protective structure that shields brain tissue from pathogens and toxic substances, maintains ionic homeostasis, and ensures nutrient supply. It is located at the level of cerebral microvessels and represents the largest interface between the brain and blood, with an estimated surface area of 12 to 18 m^2. In other words, the central nervous system (CNS) has low cellular proliferation and is protected by the BBB, which serves as a critical barrier against chemotherapeutic agents for brain tissue. The vascular endothelial tissue of the BBB exhibits a unique cellular organization compared to other tissues, providing protection against neurological complications during treatment. However, despite this protection, neurological complications such as confusion, encephalopathy, seizures, headaches, myelopathy, and vision problems can still occur during chemotherapy. The BBB is composed of endothelial cells that line the cerebral capillaries, while surrounding astrocytes, pericytes, and microglia interact with these endothelial cells to support BBB function. The BBB acts as a neurovascular gatekeeper, allowing certain molecules to pass while blocking others. Tight junctions (TJs) between endothelial cells tightly regulate permeability. Additionally, signaling pathways link astrocytes, pericytes, and neurons to endothelial cells, indirectly regulating BBB permeability by tightening or loosening these junctions, thereby altering endothelial permeability (Arvanitis et al. 2020).

The BBB also regulates the passage of drugs, including chemotherapeutic agents, into the brain. More than 98% of small molecules cannot penetrate the CNS. Only drugs that meet the criteria of Lipinski's "Rule of Five" (with a molecular weight of less than 500 Da, lipophilicity, no more than five hydrogen bond donors, no more than 10 hydrogen bond acceptors, and an octanol-water partition coefficient log P value of less than 5) possess the necessary characteristics for BBB permeability (Lipinski et al. 2001). Some chemotherapeutic agents, such as paclitaxel and 5-fluorouracil, have been shown to cross the BBB to a limited extent (Wardill et al. 2016). Furthermore, intratumoral, intrathecal, or intranasal drug administration can be used to deliver drugs directly to the brain. In certain brain regions, such as the choroid plexus and circumventricular organs, the BBB is physiologically absent, facilitating easier drug passage into the brain (Arvanitis et al. 2020).

In the presence of primary brain tumors or metastases to the brain, the structure of the BBB may change, increasing its permeability, which can affect sensitive brain tissue. Additionally, cancer tissues require increased nutrition to grow, leading to the formation of new vascular pathways with different permeability characteristics (Arvanitis et al. 2020). Many chemotherapy agents can produce reactive oxygen species (ROS), leading to oxidative stress and damaging the BBB, which can then allow these agents to enter the brain and cause further damage via the same mechanisms.

In cancer patients receiving various chemotherapy regimens, elevated peripheral cytokines have been observed, which may contribute to BBB disruption. Certain types of cancer may directly increase peripheral cytokine levels, and these cytokines can cross the BBB, activating microglia and astrocytes to release more cytokines. This cytokine activity, in turn, activates glial cells and triggers local inflammatory responses, contributing to brain tissue damage (Ren et al. 2019, Nguyen and Ehrlich 2020). One potential factor affecting BBB integrity after chemotherapy is the activation of the Toll-like receptor 4 (TLR4) transmembrane protein. TLR4 activation leads to the production of pro-inflammatory cytokines and chemokines and the activation of intracellular NF-κB

(Vaure and Liu 2014). Evidence suggests that TLR4 signaling plays a role in chemotherapy-induced neuroinflammation and neurotoxicity (Wardill et al. 2016b).

Many chemotherapeutic agents are associated with ROS production, which can cause DNA and protein damage both peripherally and in the brain (Butterfield 2014). The immune responses triggered by cancer and chemotherapy stimulate oxidative mechanisms, increasing ROS levels. ROS can induce oxidative damage to the BBB, modify tight junctions, and activate matrix metalloproteinases (Pun et al. 2009). Additionally, ROS can activate glial cells, leading to cytokine increases and further tissue damage. Elevated ROS levels in this unstable environment can also impair mitochondrial functions, leading to further damage (Tangpong et al. 2006, Tangpong et al. 2007, Moruno-Manchon et al. 2016).

DNA Damage and Related DNA Repair Errors

Chemotherapeutic drugs, particularly agents targeting DNA, can cause DNA damage in post-mitotic neurons, accelerating cellular aging and leading to cell death (Hoeijmakers 2009, Maynard et al. 2015). Post-mitotic brain cells, such as neurons, exhibit a reduced capacity for DNA repair. Certain DNA repair pathways, like mismatch repair, homologous recombination, and non-homologous end joining, are replication-associated and therefore less active in non-dividing neurons (Maynard et al. 2015). As a result, the accumulation of DNA damage caused by chemotherapy can accelerate neuronal dysfunction and death.

In neurons, which do not undergo regular cell division, the ability to repair DNA damage is limited. DNA repair processes that are more effective in proliferating cells do not function as efficiently in these non-dividing cells. This means that neurons exposed to chemotherapy-induced DNA damage are less likely to recover, which can lead to long-term cognitive impairments and accelerate neurodegeneration. Accumulation of DNA damage in neurons can disrupt synaptic function, impair learning and memory, and contribute to the pathogenesis of neurocognitive disorders. Thus, chemotherapy-induced DNA damage may be a significant factor in the development of chemo brain, exacerbating cognitive decline and impairing brain function during and after cancer treatment (Maynard et al. 2015).

Oxidative Stress and İts Effects

One of the most significant proposed mechanisms contributing to chemo brain is oxidative stress. Overactive reactive oxygen species (ROS) are closely associated with protein and DNA damage, toxicity, neuronal death, and mutations in mitochondrial proteins (Chaturvedi and Flint 2013, Valko et al. 2015). These effects become more pronounced when ROS reach excessive concentrations or when antioxidant mechanisms fail to counteract harmful reactions effectively (Popa-Wagner et al. 2013).

The brain, being a major consumer of oxygen, is particularly vulnerable to ROS attacks. Lipid peroxidation and oxidative modifications at the DNA level result in tissue and DNA damage due to excessive ROS production (Gaman et al. 2016). Many chemotherapeutic agents produce ROS, which are linked to DNA and protein damage both peripherally and centrally (Butterfield 2014). Immune responses associated with cancer and chemotherapy further trigger oxidative mechanisms, leading to increased ROS levels.

During chemotherapy, the most significant cytokine released into the plasma is TNF-alpha, which has been shown to cause direct oxidative effects on the central nervous system (CNS), leading to neuronal damage (Keeney et al. 2013). Additionally, ROS contribute to oxidative damage to the blood-brain barrier (BBB), modify tight junctions (TJs), and activate matrix metalloproteinases (Pun et al. 2009). ROS also activate glial cells, leading to an increase in cytokines and associated damage. Elevated ROS levels and an unstable environment can disrupt mitochondrial function, causing further cellular damage (Tangpong et al. 2006, Tangpong et al. 2007, Moruno-Manchon et al. 2016). In conclusion, oxidative stress plays an important role in the development of chemo brain by extensively damaging brain cells, disrupting the BBB, and triggering inflammatory and degenerative processes. Addressing oxidative stress through therapeutic interventions may be important in reducing cognitive side effects in cancer treatment.

Inflammatory Processes and Cytokine Elevation

Chronic inflammation is one of the proposed mechanisms for cognitive decline. After activation, astrocytes and microglia in the central nervous system (CNS) can produce local inflammatory cytokines. Additionally, cytokines produced in peripheral tissues can cross into brain tissue and trigger local inflammation (Gutmann 2019).

In some types of cancer, there may be a direct increase in peripheral cytokines. Chemotherapy can also lead to an increase in cytokine levels either through the death of tumor cells and damage to surrounding tissues or by direct effects (Rao et al. 2022). Elevated peripheral inflammatory cytokine levels have been detected in cancer survivors who underwent intensive chemotherapy regimens (El-Agamy et al. 2018). Some animal studies have demonstrated that chemotherapeutics can activate microglia in brain tissue, triggering cytokine release (Seigers et al. 2010, Edwardson et al. 2017). Many inflammatory cytokines can cross the blood-brain barrier (BBB) and activate microglia and astrocytes, leading to increased cytokine release (Ren et al. 2019). However, the relationship between neuroinflammation and peripheral cytokines is not yet fully understood (Nguyen and Erlich 2020).

The activation of Toll-like receptor 4 (TLR4), a transmembrane protein in the structure of the BBB, leads to the production of pro-inflammatory cytokines and chemokines, as well as the activation of intracellular NF-κB (Vaure and Liu 2014). Evidence suggests that TLR4 signaling plays a role in chemotherapy-induced neuroinflammation and neurotoxicity (Wardill et al. 2016b). Another study showed that inflammatory cytokines, including interleukin (IL) 1β and IL-6, may play a role in chemotherapy-associated cognitive decline (Cheung et al. 2015).

Inflammatory cytokines that cannot cross the BBB may adhere to endothelial cells in the brain's vascular structure and trigger other inflammatory processes, such as the production of adhesion molecules, chemokines, nitric oxide (NO), and prostaglandins. These processes can induce oxidative stress in brain tissue, leading to the production of new inflammatory cytokines and increased neuroinflammation (Rao et al. 2022). Preclinical studies have shown that Doxorubicin increases the levels of the TNF-alpha cytokine, which can easily cross the BBB, leading to increased NOS and ROS levels and oxidative stress in the mitochondria of brain tissue (El-Agamy et al. 2019).

Neurotransmitters

One of the areas evaluated in relation to the formation of "chemo brain" is the change in neurotransmitter (NT) levels and their effects. Evidence supporting the role of NTs comes from studies on catechol-O-methyltransferase (COMT) polymorphisms conducted in cancer survivors. COMT regulates the metabolism of dopamine, epinephrine, and norepinephrine (Sheldrick et al. 2008). Specifically, the COMT Val158Met polymorphism (rs4680) is linked to higher COMT enzymatic activity for the Val allele, which results in lower cortical dopamine levels (Small et al. 2011). Consequently, cancer survivors carrying at least one Val allele are at a higher risk of developing chemo brain due to lower dopamine reserves (Small et al. 2011). Another COMT variant, rs165599 G/G, also increases the risk of chemo brain in breast cancer patients (Cheng et al. 2016).

In mice, a reduction in glutamate uptake in both the cortex and dentate gyrus was observed after doxorubicin injection (Thomas et al. 2017). A decrease in dopamine release in the striatum has also been reported after carboplatin and 5-fluorouracil injections (Kaplan et al. 2016, Jarmolowicz et al. 2019). Additionally, reduced serotonin release in the raphe nucleus was reported following carboplatin injection (Kaplan et al. 2016). Increased acetylcholinesterase activity and a decrease in choline, the precursor of acetylcholine, were observed in the hippocampus of rats treated with doxorubicin (El-Agamy et al. 2018, Keeney et al. 2018). Furthermore, reduced levels of dopamine and serotonin were observed after doxorubicin injection (Du et al. 2021). These results suggest that decreased NT activity may be a contributing factor to chemo brain (Rao et al. 2022). Despite these findings, the exact mechanism of the relationship has not yet been determined. Further studies focusing on neurotransmitters are needed for different types of cancer and treatment processes.

Loss of Spinal and Dendritic Arborization

Dendrites and spines regulate synaptic plasticity, which is essential for learning, memory, and executive functions (Forrest et al. 2018). Both structures, especially spines, remain dynamic even in mature neurons, facilitating the plasticity needed for learning and adapting to new experiences. Dendrites and spines can decrease due to various factors, such as glutamate toxicity (Forrest et al. 2018). These losses can lead to cortical thinning, potentially explaining the reduction in gray matter observed in the brains of cancer survivors after chemotherapy.

Rodent models have shown that dendritic and spine complexity decreases following chemotherapy (Andres et al. 2014, Acharya et al. 2015, Groves et al. 2017, Kang et al. 2018). Additionally, a reduction in spine number and dendritic branching has been observed in the cingulate cortex (Zhou et al. 2016). Studies on the relationship

between chemo brain, chemotherapy, and arborization loss are limited, highlighting the need for more comprehensive research across broader brain regions.

Genetic Factors and Epigenetic Modulation

One of the proposed mechanisms for the pathophysiology of chemo brain is genetic predisposition. Studies involving breast cancer survivors have identified three single nucleotide polymorphisms (SNPs) that may be associated with or contribute to cognitive decline: Apolipoprotein E (APOE), Brain-Derived Neurotrophic Factor (BDNF), and Catechol-O-methyltransferase (COMT) (Cheng et al. 2016). Cancer survivors carrying the APOE e4 variant have shown cognitive deficits and reductions in hippocampal volume (Koffie et al. 2012). The BDNF Met allele appears to be protective against cognitive decline. Cancer survivors with the BDNF Val66 mutation have been found to have lower BDNF levels and are more susceptible to cognitive loss, whereas survivors with the BDNF Met allele showed no change in plasma BDNF levels (Savitz et al. 2006, Tan et al. 2019). A cross-sectional study involving cancer survivors undergoing chemotherapy reported that individuals with the COMT-Val genetic variation performed poorly in various cognitive domains. Moreover, cancer survivors with the COMT-Val variation demonstrated worse performance in attention tests compared to healthy individuals with the same genetic variation (Erickson et al. 2010, Dooley et al. 2016).

Another possible mechanism for chemo brain is the epigenetic reprogramming caused by chemotherapy, which may lead to long-lasting impairments (Wang et al. 2015). A study found that cancer survivors face multiple biological issues following chemotherapy (Heim and Binder 2012). Tumor-bearing mice exposed to chemotherapy exhibited more pronounced disruptions in post-transcriptional regulation of gene expression, particularly miRNA alterations in the prefrontal cortex. miRNA dysregulation has been associated with changes in BDNF levels (Kovalchuk et al. 2017). While evidence on the relationship between epigenetic changes and chemo brain remains limited, further research is necessary to evaluate the impact of secondary epigenetic alterations induced by chemotherapy.

Effects of Chemotherapy on Cognitive Functions

With the increasing survival rates among cancer patients due to new treatment options, improved healthcare, and early diagnosis and treatment methods, the long-term side effects of chemotherapy have garnered much more attention. Historically, the focus was primarily on chemotherapy's side effects, such as bone marrow suppression and peripheral neurotoxicity. However, in recent years, neurocognitive losses, including memory and attention issues, have become noticeable in patients undergoing chemotherapy. This shift has prompted clinicians to pay closer attention to the neurocognitive side effects of chemotherapy.

Patients often report short- and long-term complaints related to executive functions following chemotherapy treatment. This has brought attention to the adverse effects of chemotherapy on cognitive functions and led to the emergence of the concept of "chemo brain." Chemo brain, still a relatively new concept, is used to describe the short- and long-term cognitive effects of chemotherapy. An increasing number of studies on chemo brain are being added to the literature. The cognitive side effects of chemotherapy agents and strategies to reduce and prevent these side effects are becoming increasingly important (Silberfarb 1983).

Clinical Features of Chemo brain

Patients undergoing chemotherapy often report neurocognitive complaints, which in the past were primarily attributed to the stress caused by the disease itself. However, it is now believed that chemotherapy has a direct impact on cognitive functions. During the acute treatment phase, patients may experience issues such as forgetfulness and difficulty concentrating, but these complaints can also persist years after treatment. Due to the challenges of researching chemotherapy's effects on cognitive functions, no clear prevalence of cognitive impairment has been established. Studies report a wide range of rates, influenced by factors such as study design, follow-up duration, and the types of drugs administered. Nevertheless, many studies have demonstrated cognitive decline following chemotherapy (Hurria et al. 2007, Whittaker et al. 2022).

In a study by Janelsins and colleagues (2017), 36.5% of breast cancer patients who received chemotherapy showed neurocognitive impairment after one year of follow-up. Similarly, Wefel and colleagues (2010) observed long-term cognitive decline in 29% of patients. Studies on childhood cancers provide valuable insights into the long-term effects of chemotherapy on academic achievement. Children who underwent chemotherapy at an

early age often experienced declines in school performance, and neurocognitive assessments compared to their siblings revealed cognitive deficits in these patients.

Research has particularly focused on the hippocampus due to the prevalence of memory complaints. The most common cognitive complaints include difficulties with attention and concentration, as well as problems with short-term memory retrieval (Ahles and Saykin 2007, Dikerman 2007, Yang and Moon 2013). While cognitive impairments are not life-threatening, they are associated with reduced quality of life in the long term. Common complaints include memory loss, decreased attention and concentration, difficulty performing daily tasks, confusion, and mental fog. Although memory and attention problems are the most pronounced, patients may also experience declines in verbal learning, cognitive processing speed, and fine motor skills.

These clinically observed symptoms are often subjective, and may be mistakenly attributed to psychological disorders such as depression and anxiety. Although this perspective is not entirely incorrect, research has explored this question in more detail. Some studies have shown that patients' cognitive complaints are independent of depression and that neurocognitive testing reveals impairments (Hutchinson et al. 2012). While it can be challenging to distinguish between cognitive deficits caused by chemotherapy and those related to psychological conditions, existing studies suggest that chemotherapy leads to neurocognitive decline independent of mental health disorders. Cognitive decline due to chemotherapy typically manifests as subjective complaints, such as forgetfulness, inattention, and fatigue. These subtle symptoms may sometimes go unnoticed even by the patient. The patient may be experiencing cognitive decline due to chemotherapy without realizing it. At this point, physician awareness is crucial. In addition to assessing for mental health disorders, cognitive functions should be evaluated in cancer patients, including those who received treatment a long time ago. Physicians' questioning of patient symptoms is a key step in increasing awareness of chemo brain (Hutchinson et al. 2012)..

Risk Factors

Neuronal damage is one of the most well-known effects of chemotherapy agents, and it is dose-dependent. The higher the dose of the agent used and the longer the exposure duration, the greater the increase in neuronal damage, making dose and duration of treatment the most significant risk factors for cognitive decline. Among chemotherapy agents, vinca alkaloids, cisplatin, and taxane groups are known to cause the most neurotoxicity. Cisplatin damages DNA synthesis, vinca alkaloids inhibit cell division, and taxane drugs cause cell damage through microtubule polymerization. Acute side effects, such as peripheral neuropathy, encephalopathy, and CNS damage, can be so severe that they may lead to the discontinuation of treatment. Antimetabolite agents such as methotrexate, cytarabine, and fluorouracil also exhibit pronounced neurotoxic effects (Verstappen et al. 2003, Sioka and Kyritsis 2009).

Although the pathophysiology of neurotoxicity is not fully understood, halting treatment can reduce the progression of neuronal damage. In cases where discontinuing treatment is not possible, reducing the dose may help prevent further complications (Taillibert et al. 2016). It is unclear whether the development of neuropathy is a direct indicator of cognitive impairment, but it is important to monitor these patients with tests for neuronal transmission and neuropsychiatric assessments. While the dose and duration of exposure to the chemotherapy agent are the primary risk factors, individual variations in cognitive decline have also been observed. Longitudinal studies with large sample sizes are essential to better understand these risk factors and cognitive decline in patients. However, the heterogeneity of patient populations and the difficulty in conducting large-scale studies pose limitations.

Other potential risk factors include pre-treatment cognitive capacity, low socioeconomic status, and limited access to healthcare. However, due to the scarcity of longitudinal studies, there is no definitive understanding of these risk factors. In addition to sociodemographic features, factors such as the route of drug administration, concurrent radiation therapy, the presence of chronic diseases that may affect cognitive function, substance and alcohol use, and organic syndromes may also influence cognitive decline. As a result, the development of chemo brain appears to be unpredictable and varies from person to person, potentially independent of known risk factors (Zhou et al. 2024).

Neuroimaging Methods

One of the most important tools for understanding the effects of chemotherapy on neurocognitive functions is neuroimaging methods. To date, research has predominantly focused on findings related to radiation necrosis. However, many researchers have also investigated the effects of both radiation necrosis and chemotherapy on

the brain. Studies have notably reported a reduction in gray matter volume in the hippocampus. Additionally, decreases in gray and white matter volumes in the frontal cortex and frontal hypoactivation have been identified as imaging findings associated with chemotherapy use (Yağmurlu et al. 2008, Simó et al. 2013).

One study showed a reduction in gray matter volume in the prefrontal cortex, parahippocampal gyrus, and precuneus (Inagaki et al. 2007). However, some studies have failed to confirm reductions in hippocampal volume and other imaging findings (Yoshikawa et al. 2005). These inconsistencies may be due to differences in research methods and sample characteristics. Despite the lack of consistent results across studies, neuroimaging methods remain one of the most important tools for enhancing our understanding of the concept of chemo brain (Isaac et al. 2024).

Neuropsychological Tests

Cognitive impairments related to chemotherapy can sometimes be subtle enough that they are not detectable by neuropsychiatric tests. This can pose challenges in objectively assessing cognitive loss. Nevertheless, neuropsychiatric tests play a crucial role in measuring cognitive deficits associated with chemotherapy, complementing imaging methods. However, the applicability of these tests is limited by several factors, including their lengthy administration times, the impact of the patient's current condition, and variability depending on the administrator. Despite these challenges, neuropsychological test batteries such as the verbal subtests of the Wechsler Adult Intelligence Scale (e.g., digit span, arithmetic), the Wechsler Memory Scale, and the Stroop Test can be used in clinical settings to evaluate cognitive loss. It is important to assess multiple cognitive domains rather than just one, necessitating the use of sensitive tests that cover various cognitive areas. Additionally, evaluating patients' cognitive performance before, during, and after chemotherapy, as well as in the long term, is essential for demonstrating cognitive decline associated with chemotherapy (Marín et al. 2009).

Treatment Approaches to Chemo Brain

There are currently no established diagnostic criteria or approved treatments for chemotherapy induced cognitive impairments, also known as "chemo brain." Chemo brain presents with many confounding factors, such as genetic variability, treatment regimens, and comorbidities with other neuropsychiatric disorders, resulting in a highly heterogeneous clinical presentation. Since there is no clear disease mechanism, the effects of different agents on treatment are still being investigated. In this section, studies on treatment approaches will be summarized in light of the current literature. Studies on pharmacological treatments for chemo brain are presented in Table 1, while non-pharmacological methods are listed in Table 2. Treatment options targeting the prominent pathological mechanisms in the treatment of chemo brain are still being developed. Currently, treatments aimed to regulate neurogenesis and gliogenesis include exercise, lithium, selective serotonin reuptake inhibitors (SSRIs), and stem cell transplantation. Agents targeting the loss of dendritic spines include metformin and phosphodiesterase inhibitors (PDEIs). Agents that act on neurotransmitters important for cognitive function, such as acetylcholine and glutamate, include acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists. PLX5622 and LM22A-4 are being studied to treat glial cell dysfunction, while anti-inflammatory and antioxidant agents are highlighted for reducing inflammation (Nguyen and Ehrlich 2020). However, no study has yet identified a fully effective and safe treatment agent. The current literature emphasizes the need for well-defined animal models of cognitive dysfunction to investigate the detailed mechanisms that lead to chemo brain, as well as well-designed clinical trials to identify drug targets and their therapeutic significance for more effective outcomes. Additionally, the use of standardized terminology and measurement tools in studies will enhance the reliability of data. Along with the pharmacological agents being developed, it has been suggested that behavioral approaches aimed at optimizing modifiable factors (such as sleep, diet, stress, and exercise) could lead to subjective improvements.

Table 1. Studies on pharmacological approaches in chemo brain treatment

Drug Groups	Mechanisms of Action	Drug	Study Results
Anti-dementia Treatment	AChEI	DPZ GAL	In animal studies, it has been shown that with the inclusion of DPZ in the treatment, cognitive dysfunctions caused by DOX (Ongnok et al.2021), MTX +5-FU (Winocur et al.2011), and TRZ (Khuanjing et al.2023) are reduced/improved. There is a study suggesting that DPZ treatment would be beneficial in the treatment of cognitive impairment caused by DOX and CP (Lim et al.

			2016), while there is a more recent study showing that it is not effective (Philpot et al. 2019). Although findings on the positive effects of adding DPZ treatment to protective factors in the treatment of chemotherapy have been presented (Winocur 2017), it has also been emphasized that it does not reduce the effectiveness of antitumoral drugs. In addition to animal studies, in a placebo-controlled 36-week follow-up study of 62 women who had received chemotherapy for breast cancer 1-5 years ago and had symptoms of cognitive impairment, the DPZ group performed significantly better than the control group on the Total Recall (p = 0.033) and Discrimination (p = 0.036) subscales of the Hopkins Verbal Learning Test-Revised (HVLT-R) (Lawrence et al. 2016). Although DPZ has been used in most studies, GAL has also been shown to be a neuroprotective agent against DOX-induced neuroinflammation by reducing inflammatory markers in the brain (Alsikhan et al. 2023).
	NMDAR Antagonism	Memantıne	When the effects of different memantine regimens on neurogenesis and inflammation were evaluated in the chemobrain model obtained by administering PTX to eight-week-old male B6 mice, it was shown that both pretreatment and co-treatment regimens successfully reversed impaired neurogenesis and spatial memory impairment in behavioral tests (Sung et al. 2021).
	AMPAR PAM	Pırasetam (PIRA)	It has been shown that PIRA has neuroprotective activity against DOX-induced cognitive deficits, and it has been emphasized that this may be linked to the reduction of AChE levels, neuro-inflammatory mediators, pro-apoptotic proteins and oxidative stress (Mani et al. 2022a).
Psychotrops	Antidepressants	Fluoksetine Fluvoksamine Sertraline	A study in male Lister rats showed that MTX caused an impairment in spatial working memory and had a long-term negative effect on hippocampal neurogenesis, which was counteracted by the co-administration of fluoxetine (Lyons et al. 2011), while a different study showed that fluoxetine could prevent but not reverse the cognitive and cellular effects of 5-FU (Lyons et al. 2012). While increased anxiety-like behaviors and cognitive impairment were observed in mice treated with radiation and TMZ, it was shown that chronic fluoxetine administration could reverse behavioral dysfunction. It has been stated that the effect of fluoxetine may be through the rescue of neurogenesis deficit caused by radiation and TMZ treatment (Gan et al. 2019). In addition to fluoxetine, fluvoxamine has also been shown to attenuate PTX-induced neurotoxicity, in part through induction of Sig-1R (Tanimukai and Kudo 2015). In a controlled study investigating the effects of sertraline on executive functions and quality of life in 122 advanced cancer patients, it was concluded that it could improve executive functions and quality of life (Li X et al. 2014).
	Antipsychotics	Amisulpride	In a study investigating the effects of amisulpride treatment in the treatment of 5-FU-induced cognitive deficits in Wistar rats, amisulpride enhanced Wnt/GSK-3β/β-catenin signaling, increased BDNF levels, and eliminated 5-FU-induced neuroinflammation, apoptosis, β-amyloid accumulation, and neurodegenerative changes, thereby improving cognitive performance. This study highlighted the pro-cognitive effects of amisulpride, which can be attributed to the enhancement of the hippocampal Wnt/GSK-3β/β-catenin signaling pathway in rats exposed to 5-FU, and emphasized that it may be a promising therapeutic option for chemobrain (Rafat et al.2023).
	Mood Stabilizers (MS)	Lithium	Lithium has been used for years in psychiatric disorders, but recently evidence has emerged for its neuroprotective effects. Treatment of mice with lithium prevented PTX-induced memory deficits and abnormal adult hippocampal neurogenesis (Huehnchen et al.2022). Although lithium appears promising in preclinical studies, its utility as a neuroprotectant in patients undergoing cancer treatment has not yet been confirmed.

		D-methylphenıdate (d-MPH)	In a randomized controlled trial in which women receiving adjuvant chemotherapy for breast cancer were treated with d-MPH or placebo, patients were screened with the High Sensitivity Cognitive Screening (HSCS) and the HVLT-R, the Global Functional Assessment of Cancer Therapy questionnaire, at approximately 6 months follow-up. No significant difference was detected between the groups in any evaluation, but the power of this study was found to be insufficient (Mar Fan et al. 2008).
		Modafınıl	Modafinil has been found to improve cognitive performance by improving some memory and attention skills in women who survived breast cancer (Kohli et al.2009).
Antiepileptic Drugs		Levetiracetam (LEVE)	LEVE application has been shown to improve DOX-induced memory-related parameters in animals, and it has been suggested that this 'Nootropic-like' activity may be associated with decreased AChE and decreased neuroinflammatory marker levels (Mani et al.2022b).
Antidiabetic Treatment	AMP-activation of activated protein kinase	Metformine	Metformin, a biguanide antihyperglycemic, is a widely used safe agent. Animal studies have shown that it is effective in cisplatin and PTX-induced cognitive impairment (Zhou et al. 2016; Khodabakhsh et al. 2024), but it cannot improve cognitive impairment caused by DOX (Alharbi et al. 2020).
	PPAR-g activation	Piaglitazone (PIO)	PIO, an insulin-sensitizing diabetes drug, has been shown to improve DOX-induced cognitive impairment by modulating the expression of inflammatory cytokines and alleviating neuronal inflammation, and has been presented as a promising treatment for chemobrain (Alhowail 2024; Alsaud et al. 2023).
	DPP-4 inhibitor	Vildagliptin (VİLDA)	VILDA, which has shown promising neuroprotective properties against various neurological diseases, has been shown to increase cholinergic neurotransmission, inhibit neuroinflammation, and increase hippocampal neurogenesis through downregulation of the AChE enzyme in an animal study investigating its potential neuroprotective properties against CP-induced neurotoxicity. It has been stated that these effects are mainly mediated by the activation of AMPK/Akt/CREB signaling cascades (Mahmoud and 2023).
Anti-Inflammatory / Antioxidant Agents		COX Inhibition	Since inflammation is one of the several neural mechanisms proposed to explain chemobrain, the efficacy of anti-inflammatory agents has been frequently tested. In a systematic review of 64 studies, 41 out of 50 anti-inflammatory agents (82%) were reported to reduce chemobrain, and heterogeneity was observed in terms of the methods used (Haller et al.2023). It has been reported that NS398, a selective cyclooxygenase-2 (COX-2) inhibitor anti-inflammatory agent, prevents chemobrain in vivo without adversely affecting the antitumor efficacy of cisplatin or aggravating tumor growth (Rashid et al.2023). In a study using an autotopic mouse model of breast cancer, mice with breast tumors had significantly poorer memory than mice without tumors, and this memory impairment was independent of cancer-induced sickness behavior and was observed in mice with high metastatic burden at later stages of cancer progression. The memory impairment attributed to proinflammatory cytokines secreted by the tumor was completely stopped by oral treatment with low-dose aspirin (Walker et al. 2018). However, in a different animal study, PTX-induced memory impairment was not improved by aspirin treatment. This finding was explained by the fact that inflammation may not be responsible for PTX-induced memory impairment or that it may result from multiple convergent mechanisms (Chang et al. 2020).
		Cerebrolysinn (CBN)	CBN, a mixture of various neurotrophic factors and active peptides with anti-inflammatory, antioxidant and neuroprotective effects, significantly and dose-dependently improved cognitive functions, reduced oxidative stress markers, inflammatory cytokines and restored neurotransmitter concentration in a BCNU-induced cognitive impairment model in mice (Sharma et al. 2022).

Antilipid Drugs Diuretics		Chrysin	Chrysin-5,7 dihydroxyflavone has promising antioxidant, anti-inflammatory and anticancer properties but has low bioavailability due to its poor solubility and extensive metabolism. Intranasal administration of optimized chrysin formulations at a reduced dose of 0.5 mg/kg ameliorated DOX-induced memory impairment in rats as evidenced by behavioral tests, AChEI and oxidative stress markers (Ibrahim et al.2021).
		FA-Leu SD	Ferulic acid (FA), a natural polyphenol, has been confirmed to have nootropic, neuroprotective and antioxidant effects. FA-Leu SD equivalent to 150 mg/kg free FA provided better results than FA alone in reducing oxidative stress and improving DOX-induced cognitive impairment (Shukla et al.2024).
		MCC950	The role of the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome in cognitive impairment caused by chemotherapeutic agents commonly used in breast cancer has been highlighted. When rats in which chemobrain model was established with DOX and CP were treated with the NLRP3 inhibitor MCC950, cognitive impairment was significantly reduced (Jia et al.2023).
		Alpha Lipoic Acid (ALA)	Alpha-lipoic acid (ALA), a dietary supplement, is known for its antioxidant, anti-inflammatory, and anti-apoptotic activities. In an animal study, ALA treatment significantly protected against DOX-induced memory impairment. This result was attributed to the antioxidant potential of ALA via the NRF-2/HO-1 signaling pathway (Lal et al. 2023).
		N-Acetylcysteine (NAC)	The cognitive impairment and decrease in the hippocampal GSH/GSSG ratio caused by combined treatment of DOX and CP once a week for 2 weeks in mice were reversed by NAC (Kitamura et al. 2021).
		C-Phycocyanine (CF)	CF is an agent that has been shown to have strong anti-inflammatory, antioxidant, and mitochondrial protective properties. In animal experiments, CF suppressed DOX-induced neuroinflammation and oxidative stress, alleviated mitochondrial abnormalities, and ameliorated DOX-induced cognitive deficits by increasing synaptic density in the hippocampus of mice (Wang et al. 2021).
		MESNA	Mesna is a chemoprotective agent with anti-inflammatory and antioxidant effects. It has been demonstrated that cisplatin-induced central and peripheral nervous system toxicity can be alleviated by Mesna (150 mg/kg/day) treatment in male Wistar rats after 2.5 mg/kg cisplatin administration twice a week for four consecutive weeks (Saadati et al.2021).
		Caffeic Acid Phenyl Ester (CAPE)	CAPE is a pro-oxidant in cancer cells, while it is a strong antioxidant and cytoprotective agent in normal cells. The potential neuroprotective effects of CAPE against DOX-induced cognitive impairment were investigated in Sprague Dawley rats. Co-treatment with CAPE significantly prevented behavioral and molecular abnormalities caused by DOX in the rat brain, and evidence was presented that CAPE has promising neuroprotective activity against neurodegeneration and memory deficits (Ali MA et al.2020).
		IFN-β-1a or Infliximab	IFN-β-1a or Infliximab ameliorated DOX-induced hippocampal histopathological neurodegenerative changes in animal experiments, stopped cognitive impairment, eliminated mitochondrial oxidative, inflammatory and apoptotic stress, and alleviated autophagic dysfunction. These findings indicated that Infliximab provided neuroprotection against DOX-induced chemobrain, which can be explained by its antioxidant, anti-inflammatory, pro-autophagic, pro-mitophagic and antiapoptotic effects (Wahdan et al. 2020).
		Cyclosporine A (CsA)	CsA has been confirmed to have a neuroprotective role during MTX-induced cognitive impairment, and the possible underlying mechanisms have been suggested to mediate the translocation of HuR and alleviate neuroinflammation and neuronal apoptosis via NCOA4-mediated ferritinophagy (Ding et al. 2023).

		L carnitine	L carnitine, known to have antioxidant and anti-inflammatory activities, has been reported to exhibit neuroprotective effects by reducing AChE activity against DOX and CP-induced chemobrain in rats (Morid et al. 2023).
		Atorvastatin (ATV)	ATV exhibited neuroprotective properties against cognitive impairment induced by TZB (Lee et al. 2021) and DOX (Mounier et al. 2021), probably through its anti-inflammatory, antioxidant and anti-apoptotic effects in the brain.
		Amylorid (AML)	AML, an antihypertensive, potassium-sparing diuretic that has been proven to be neuroprotective in different experimental models, significantly attenuated DOX-induced neurodegeneration and memory impairment in mice after 4 weeks of treatment (Ali et al. 2022).
	Adenosine 2a Rsp (A2AR) Blockade	KW-6002	Cisplatin has been shown to increase the A2AR and its downstream effectors cAMP and CREB, which are important for learning, in the adult mouse hippocampus. Inhibition of A2AR by FDA-approved KW-6002 prevented cisplatin-induced impairments in neuronal proliferation and dendrite morphogenesis, while reducing memory impairment (Oliveros et al.2022).
	Adenosine 3 Rsp (A3R) Agonist	MRS5980	When the capacity of a highly selective A3R agonist, MRS5980, to prevent and reverse cisplatin-induced neurotoxicities was investigated, it was shown to prevent cisplatin-induced cognitive impairment such as decreased executive function, spatial and working memory impairment, sensory motor impairments and neuropathic pain in both genders (Singh et al. 2022).
	Histaminergic 1 receptor (H1R) antagonist	Clemastin	Clemastine improved cognitive functions and white matter damage, strengthened myelination, promoted oligodendrocyte precursor cell differentiation, and increased neurofilament 200 protein levels in the corpus callosum and hippocampus in chemotherapy-treated mice. It has been suggested that clemastine improves cognitive function damage with these effects (Chen et al.2022).
	a2 – adrenergic receptor agonist	Dexmethodomidine (DEX)	DEX protected HT22 cells against MTX-induced neurotoxicity through changes in nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy (Chen et al.2021). It has also been suggested that DEX alleviates cisplatin-induced cognitive impairment by modulating miR-429-3p expression in rats (Li et al.2020).
PDEI's	Phosphodiesterase Inhibitor (PDEI)	Roliprame Ibudilast	DOX-treated rats exhibited changes in spatial memory and depressive-like behavior, but these symptoms were reversed after chronic rolipram administration (Callaghan et al. 2015). In a separate study, ibudilast treatment before oxaliplatin prevented the development of tactile allodynia and memory deficits in rats (Johnston et al. 2017).
Nicotinic and Muscarinic Acetylcholine Receptor Agonists			Male Wistar rats were treated with six doses of DOX via intraperitoneal injection to create a chemobrain model and treated with α7nAChR agonist (PNU-282987: 3 mg/kg/day), mAChR agonists (bethanechol: 12 mg/kg/day) or both in combination. DOX administration led to cognitive dysfunction via neuroinflammation, glial activation, decreased synaptic/blood-brain barrier integrity, and defective mitochondrial ROS detoxification capacity. PNU-282987, bethanechol or combined treatment improved cognitive function by suppressing excessive apoptosis, necroptosis, and pyroptosis. The findings showed that AChR agonists effectively protected against DOX-induced neuronal death and chemobrain (Ongnok et al. 2024). In a pilot study, when transdermal nicotine was compared with placebo in women with cancer-related cognitive impairment, no significant difference was found between the two groups in terms of remission of cognitive impairment (Vega et al.2019).
	NAD+ Precursor	Nicotinamide Mono Nucleotide (NMN)	It has been shown that increased mitochondrial oxidative stress and functional disorders may play a key role in cisplatin-induced neurotoxicity. It has been presented that NMN may be an effective therapeutic strategy to prevent the harmful effects of cisplatin on mitochondria, may become a key factor in improving cisplatin-induced cognitive impairments, and may provide hope for

			improving the quality of life in cancer survivors (Rashid et al.2022; Yoo et al. 2021).
	BDNF enhancer	Riluzole (RZ)	In clinical studies, decreased blood levels of BDNF in breast cancer patients treated with DOX were associated with the risk of chemobrain. When the effect of RZ, an orally active BDNF-enhancing drug, was investigated on mice treated with DOX, it was reported to attenuate the immature neuronal loss and neuroinflammation caused by chemotherapy. It was stated that preclinical evidence was provided for a translationally applicable approach to enhance the neuroprotective effects of RZ treatment to prevent chemobrain (Usmani et al.2023).
Vitamins		Vitamine E (Vit E)	A potential role of Vit E has been shown in alleviating short-term memory impairment in rats exposed to DOX and PTX chemotherapy, probably by reducing hippocampal oxidative stress and neurodegeneration (Altarifi et al.2024).
		Calcitriol	Co-administration of calcitriol has been shown to prevent cisplatin-induced behavioral and cognitive impairments in rats, attenuate cisplatin-induced decreased hippocampal BDNF levels, and upregulate BDNF mRNA in the hippocampus. Increased hippocampal BDNF is thought to mediate the beneficial effects of calcitriol against neurotoxicity in cisplatin-exposed rats (Abdollahzadeh et al. 2022).
		Bexaroten	Bexarotene has also been shown to activate the neuregulin and netrin pathways, which play a role in myelin formation/maintenance, synaptic function, and axonal guidance. Short-term treatment with bexarotene was found to be sufficient to reverse the adverse effects of cisplatin on white matter structure, cognitive function, and sensorimotor performance (Chiang et al.2020).
		Probiotic Supplement	In a randomized, double-blind, and placebo-controlled study on 159 patients with breast cancer, probiotic supplementation significantly reduced the incidence of chemobrain and improved general cognitive functions by modulating plasma metabolites, including p-Mentha-1,8-dien-7-ol (Juan et al.2022).
		7-chloro-4-(phenylselanyl)quinoline (4-PSQ)	4-PSQ reduced OXA-induced cognitive impairment in mice due to modulation of Na+K+-ATPase and reduction of corticosterone levels (Reis et al. 2020).
	Inhibitor of histone deacetylase 6 (HDAC6)	ACY-1215 (Ricolinostat)	When the effect of HDAC6 inhibitor ACY-1215 on cisplatin-induced brain damage and cognitive impairments in mice was examined, it was shown to improve behavioral disorders, dendritic loss and increase synaptic density. It was also shown to increase α-tubulin acetylation in the hippocampus of mice, and to correct cisplatin-induced impaired mitochondrial transport and mitochondrial dysfunction in the hippocampus (Wang et al. 2019). A similar study concluded that HDAC6 inhibitors appear to be a promising therapeutic approach to reverse chemotherapy-induced neurotoxicity while enhancing tumor control (Ma et al. 2016).
		Ginseng	The potential effect of ginseng in the prevention and treatment of neurological diseases has been shown in many studies over the years. In a study conducted with male rats, ginseng, which can eliminate cisplatin-induced memory impairment, has been shown to restore neurological efficiency by reducing oxidative stress and neuroinflammation (Hussien et al. 2022). Ginsenoside rg1, a ginseng-derived compound, significantly improved chemobrain-like behavior in the water maze test in a chemobrain mouse model induced by docetaxel, adriamycin, and cyclophosphamide (DAC) injection. In vivo neuroimaging has shown that rg1 treatment reversed DAC-induced decreases in prefrontal and hippocampal neuro-

			nal activity and improved cortical neuronal dendritic spine elimination. At the same time, rg1 suppressed the increase in proinflammatory cytokines and increased the levels of anti-inflammatory cytokines. These results suggest that rg1 exerts its anti-chemobrain effect by promoting neuroplasticity, particularly in brain regions associated with cognitive processing, in conjunction with the inhibition of neuroinflammation (Shi et al. 2019).
	Ribonucleotide Reductase Inhibitor	PAN-811	Co-administration of PAN-811, a ribonucleotide reductase inhibitor, significantly reduced all cognitive impairments caused by MTX/5-FU (Jiang et al.2018) .
		KU-32	There is little evidence for pharmacological treatments that can target mitochondrial dysfunction. A study evaluating the preventive effects of KU32 on the behavior of 5-FU-treated rats showed promise in preventing chemotherapy-induced impairments in temporal discrimination (Sofis et al. 2017).
Compounds that have been studied for their effects on chemobrain treatment, most of which are flavonoids, are included in this section. Polydatin (PLD) suppressed DOX-induced oxidative stress by increasing Nrf2, inhibited the inflammatory response by activating the NF-κB pathway, reduced hippocampal apoptosis, and was shown to provide neuroprotection against DOX-induced chemobrain (Tong et al. 2020). Hypericum perforatum L (HP L) and its nanoemulsion (NE) treatment has been shown to cause an increase in antioxidant defense systems against cisplatin-induced neurotoxicity and a decrease in pro-inflammatory cytokine levels, resulting in improved motor activity and spatial working memory in rats (Khalil et al. 2023). In the chemobrain model created by DAC injection in mice, resveratrol reduced chemobrain with cytokine modulation and neuroprotective effects (Shi et al. 2018). Catechin, known as tea polyphenols, are chemopreventive agents. Catechin has been shown to prevent DOX-induced memory impairment with its antioxidant, anti-inflammatory and AchE inhibition effects (Cheruku et al.2018). Galangin (GAL), which has significant protective effects in various neurological disorders, has been advocated for simultaneous use to manage DOX-induced neurodegeneration and cognitive/behavioral deficits (Abd El-Aal et al. 2022) Juglanin (JUG) is a flavonoid with antioxidant, anti-inflammatory, neuroprotective and anticancer properties. It has been suggested that JUG provides neurological protection against DOX-induced chemobrain by ameliorating oxidative stress and inflammation in rats (Wei et al. 2022). Berberine (BBR) has been emphasized to cause neuroprotection against DOX-induced cognitive decline by modulating brain growth factors and exerting anti-inflammatory, anti-apoptotic and anti-oxidative effects (Shaker et al. 2021). Curcumin has been shown to improve impaired cognitive behaviors in cisplatin-treated C57BL/6 mice, and cognitive recovery has been shown to be mediated by increasing hippocampal autophagy (Yi et al. 2024). Naringin treatment has been shown to significantly and dose-dependently prevent all behavioral, biochemical and molecular changes in cisplatin-treated aged rats (Chtourou et al. 2016). When the potential adverse effects of kolaviron (KV), a neuroactive extract rich in flavonoids with anti-oxido-inflammatory and anti-apoptotic properties, on busulfan-induced oxidative damage, inflammatory proteins and apoptosis in the brain were investigated, it was revealed that it prevented busulfan-induced cognitive and testicular disorders (Tesi et al.2022). Concomitant administration with Rutin (RUT) provided protection against DOX-induced myelosuppression, cardiotoxicity, and nephrotoxicity, suggesting that it may be a possible adjuvant therapeutic intervention to alleviate cognitive and other complications associated with DOX chemotherapy (Ramalingayya et al. 2017). When the effects of ganoderic acid (GA), isolated from Ganoderma lucidum, which has been observed to have neuroprotective effects, were examined against 5-FU-induced cognitive dysfunction, it was shown to significantly prevent the decrease in spatial and non-spatial memory in mice. It has been shown that GA can prevent cognitive dysfunction in 5-FU-treated mice by preventing mitochondrial degradation and enhancing neuronal survival and growth (Abulizi et al. 2021). Resveratrol (RSV) or curcumin (CUR) prevented memory loss, astrogliosis, and microgliosis caused by DOX monotherapy in mice (Moretti et al. 2021). Kai-Xin-San (KXS) reduced DOX-induced cognitive impairment by regulating inflammatory responses, reducing oxidative stress, and neural degeneration (Lyu et al. 2021). It has been concluded that Oroxylum indicum extract (OIE) prevented chemobrain by eliminating oxidative stress and perhaps improving mitochondrial function in cognitive impairments due to DOX and CP chemotherapy (Pondugula et al. 2021).			

CP: cyclophosphamide, DOX: doxorubicin, CsA: cyclosporine A, MTX: Methotrexate, 5-FU: 5-fluorouracil, TRZ: transtuzumab, PTX: paclitaxel, TMZ: temozolomide, BCNU: Carmustine, OXA: oxaliptine, FA-Leu SD: Amorphous ferulic acid-loaded leucine solid dispersion, DPZ: donepezil, GAL: galantamine, AchEI: acetylcholine esterase inhibitor, PIO: pioglitazone

Table 2. Studies on non-pharmacological approaches to chemobrain treatment	
Method	**Study Results**
Psychoeducation	Abnormal perceptions of cognitive difficulties have distressing consequences. Validation of cognitive concerns may help normalize chemotherapy and facilitate coping. It is recommended that the patient be advised to use helpful adaptive strategies, such as using organizational aids (e.g., lists, note-taking), finding mentally stimulating activities, adjusting expectations, and seeking help when needed. The ease of implementation of psychoeducation and its lack of cost provide a great advantage.
Physical Activity	It is thought that exercise may have an important role in improving cognitive dysfunctions, especially in cancer patients undergoing chemotherapy. It was observed that rats treated with 5-FU/OXA and exercising had improved cognitive abilities compared to rats that did not exercise (Fardell et al. 2012). Exercise also attenuated neuroplasticity and mitochondrial dysfunction in rats under DOX treatment (Park et al. 2018), while it reduced proinflammatory cytokines in eight-week-old C57BL6 mice treated with cisplatin (Park et al. 2024), and a recent study has shown that it plays a potential role in improving cognitive decline (Elbeltagy et al. 2024). However, there is still limited evidence supporting its effect in chemotherapy- and cancer-related cognitive dysfunctions as primary outcomes. Future studies are needed to confirm the possible role of exercise, including self-reported and objective measurements (Campbell et al. 2020).
Cognitive Rehabilitation	Cognitive rehabilitation has been shown to improve cognitive deficits in breast cancer patients (Park et al. 2017). Current evidence supports the clinical application of cognitive rehabilitation to improve chemobrain, but further studies on program development, dissemination and feasibility are recommended (Fernandes et al. 2019).
Web-Based Cognitive Rehabilitation Program	In a study of adult cancer survivors who had completed three or more courses of adjuvant chemotherapy within 6 to 60 months and reported persistent cognitive symptoms, the Web-Based Cognitive Rehabilitation Program led to improvements in cognitive symptoms compared with standard care (Bray et al. 2017).
Gamma Entrainment Using Sensory Stimuli (GENUS)	A noninvasive sensory stimulation treatment called GENUS has been shown to promote oligodendrocyte survival and improve cognitive function in cisplatin-treated mice, and these positive effects persisted for up to 105 days after GENUS treatment (Kim et al. 2024).
Transcrannial Magnetic Stiimulation (TMS)	The first patient presentation in a phase 1 clinical trial testing of TMS for the treatment of chemobrain demonstrated that TMS can be safely administered to individuals with chemobrain with no significant side effects. The individual with mild cognitive impairment before treatment objectively returned to normal after TMS (Kuo et al. 2023).
Stem Cell Transplantation	Mitochondria coated with dextran-triphenylphosphonium polymer administered intranasally can be rapidly detected in macrophages in the brain meninges but do not reach the brain parenchyma. Coated mitochondria alter the expression of over 2400 genes regulating immune, neuronal, endocrine, and vascular pathways in the meninges of mice treated with cisplatin. Nasal administration of coated mitochondria reversed cisplatin-induced cognitive deficits and relieved neuropathic pain (Alexander et al. 2021). In a similar study, two nasal administrations of mitochondria isolated from human mesenchymal stem cells restored cisplatin-induced executive function, working, and spatial memory deficits (Alexander et al. 2022). It has been emphasized that nasal administration of mesenchymal stem cells may represent a potent, non-invasive and safe regenerative therapy for the resolution of cisplatin-induced chemobrain (Chiu et al. 2018).
EEG biofeedback	A study of 23 female breast cancer survivors with self-reported cognitive impairment 6 to 60 months after chemotherapy showed that EEG biofeedback has the potential to reduce the negative cognitive and emotional consequences of cancer treatment, as well as improve fatigue and sleep patterns (Alvarez et al. 2013).
Managing Cancer and Living Meaningfully (CALM) intervention	CALM intervention attenuated chemotherapy in breast cancer survivors (Yao et al.2023)

Conclusion

With the advent of new treatment options, improved healthcare services, and advancements in early diagnosis and treatment methods, cancer survival rates have significantly increased. Consequently, the long-term side effects of chemotherapy have garnered much more attention. Historically, the focus of chemotherapy was primarily on side effects such as bone marrow suppression and peripheral neurotoxicity. Recently, however, the cognitive deficits associated with chemotherapy, such as memory and attention problems, have come into focus. This has prompted clinicians to concentrate on the neurocognitive side effects of chemotherapy.

Patients often experience both short-term and long-term complaints related to executive functions after chemotherapy. This highlights the need to address the adverse effects of chemotherapy on cognitive functions. The concept of "chemo brain," a relatively new term, has been introduced to describe the impact of chemotherapy on cognitive functions both in the short and long term. An increasing number of studies are being added to the literature concerning chemo brain. The cognitive side effects of chemotherapy agents and strategies to mitigate and prevent these effects are becoming increasingly important. Raising awareness among clinicians about this issue will aid in preserving the cognitive functions of patients undergoing chemotherapy.

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