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Chemotherapy and Cognition: Insights and Impacts

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ABSTRACT:

Cancer and its treatments often come with a myriad of challenges that extend beyond the physical manifestations of the disease itself. Among these challenges is the phenomenon colloquially referred to as "chemo fog" or "chemo brain," which encompasses a range of cognitive impairments experienced by cancer patients undergoing chemotherapy. Concurrently, emerging research has brought attention to the intricate interplay between mitochondria, the blood-brain barrier (BBB), and the gut-brain axis in the context of cancer and cognitive function. In this review, we embark on an exploration of the complex relationship between chemo fog, mitochondrial dysfunction, BBB integrity and the gut-brain axis in the setting of cancer. By unravelling the underlying mechanisms and elucidating their interconnectedness, we aim to provide a comprehensive understanding of the cognitive complications associated with cancer and its treatment modalities.

Introduction

In the past century, three major developments have resulted in establishment of cancer treatment: the discovery of X-rays by Wilhelm Konrad Roentgen; the utilization of transplantable animal tumor models for cancer research; and the development of the radical mastectomy, the first surgical procedure, by Halsted. The word “chemotherapy” is credited to the German chemist Paul Ehrlich, who explored the usage of medications to cure infectious illnesses. Historical accounts indicate that the use of arsenical dates to the 1900s. [1] Radiotherapy as well as surgery had been the mainstays of cancer treatment since1960s. When it became apparent that cancer might recur after radiation therapy as well as surgery and develop micro metastases, chemotherapy & combination chemotherapy began to take on importance. [2]

Chemotherapy brings on cognitive alterations, according to research done in 1980 by Dr. Peter Silberfarb et al. Surprisingly, individuals who were not getting chemotherapy targeted at the central nervous system also show signs of cognitive loss. [3] This was unexpected because most of the medications used in this study are known to not deface the blood-brain barrier. The foggy mental condition that certain cancer victims suffer following treatment has been dubbed as "chemo brain" or "chemo fog." Lack of focus, forgetfulness, vertigo, and trouble recalling events are frequently reported symptoms of chemotherapy, although long-term memory loss has not been reported.[4] Reports of chemo fog symptoms have varied because of inconsistent neuropsychological testing as well as statistical concerns as chemo brain symptoms can last anywhere from a few months to several years [5] approximately one-third of subject’s report side effects continuing for months or even up to five or ten years after treatment ends. [6] therefore, possible biological processes that underlie the chemobrain include inflammation allied with oxidative damage brought on by chemotherapy, and dysfunctional mitochondria.

RECENT RESEARCH FINDINGS ON CHEMO BRAIN

A growing body of research has reported that patients undergoing cancer treatment often experience some

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degree of cognitive decline and varies widely, ranging from 16% to 75% of patients. Downie et al [7] noted short-term memory deficits, an elongation of the information retrieval time as well as challenges with concentration, verbal fluency, word research, processing speed and spatial orientation.

The Oncology Nursing Society guidelines state that cognitive training is a more highly recommended intervention than other clinical approaches due to its effectiveness. [8] According to recent reviews, brain training as well as cognitive behavioral therapy appear more promising than other interventions. It is helpful to comprehend the mechanisms behind the impacts of interventions to increase their effectiveness through a variety of intricate mechanisms.[9] Moreover, insulin-like growth factor-1 is elevated by cognitive training that combined exercise and cognitive games, that might account for its impacts. Efficacy of pharmacological therapies are still debatable, but as their mechanisms of action are understood, they might aid in the creation of both nonpharmacological as well as pharmacological strategies.

It is important to emphasize that a cognitive deficit may be identified following a cancer diagnosis but prior to initiating medication as well as during or following chemotherapy treatment. Therefore, the possibility that cancer itself might be good enough reason for the emergence of cognitive manifestations cannot be ruled out. The way that people react psychologically to a cancer diagnosis might also affect how well they think. When a cancer diagnosis is made, anxiety and sadness are common and can either cause or contribute to chemobrain. Hurria et al [11] point out that forty-one percent of older cancer sufferers experience severe difficulty in this regard, indicating that anxiety as well as sadness may be risk indicators for cognitive impairment among cancer sufferers.

From a neurological perspective, chemotherapy as well as cancer may modify white and grey matter, changing the structure and function of the brain and shrinking the frontal and temporal cortex. [12] The chemotherapeutic drugs may be detrimental to brain cells and blood vessels directly or indirectly. Hormonal alterations remain to be investigated as one of the potential causes and processes of chemo fog. It has been observed that women receiving hormone therapy in addition to chemotherapy really have an impact to decline the cognitive abilities. Additionally, many chemotherapeutic agents often do not pass the blood-brain barrier. [13] Nonetheless, certain animal trials have demonstrated that extremely low dosages of chemotherapy agents also can result in cell necrosis as well as decrease in brain cell division those are crucial to cognition.[14]

Studies on how different cancer treatments affect the brain are beginning to pick up steam in research. Specifically, with that certain immunotherapeutic agent, particularly when used in combination, may raise the risk of severe toxicity and are linked to higher treatment-related mortality when used in conjunction with biological therapy or chemotherapy as opposed to when used alone. [15] Furthermore, there appears to be a link between immunotherapy and cognitive alterations in cancer sufferers. [16] immunotherapy appears to be a cause of several disorders affecting every part of the central as well as peripheral nervous systems. Immunotherapy targets the patient's immune system rather than the tumor directly, enhancing its ability to fight cancer by increasing tumor-responsive T cells and providing external signals for immune activation while countering regulatory mechanisms.[17] It also has been reported that though combination of immunotherapy is beneficial during oncological treatments, it is critical to note their adversative influence on normal cells, especially on neuronal cells. [18]

However, some studies report no significant cognitive changes from chemotherapy, though most chemotherapeutic agents cause neurotoxicity. [19] Despite evidence of both acute and long-term neurotoxic effects, the molecular mechanisms remain unclear. Chemotherapy’s dose-dependent neurotoxicity impacts brain regions like the hippocampus, basal ganglia, and cortex. [20] Thiotepa and methotrexate have been shown to inhibit hippocampal cell proliferation, with methotrexate also reducing cognitive function. [21] In a study by Ahamad H A has been reported that observed cognitive changes are due to increased expression AMPAR and NMDAR, are the roots of the neuronal changes, inflammation and apoptosis along with oxidative stress. [22]

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MICROBIOTA-GUT-BRAIN AXIS CHANGES

Changes in the microbiota-gut-brain axis is one of the major causes of chemotherapy-induced cognitive impairment [CICI]. It is agreed that chemotherapy disrupts the GIT microbiota, the extensive linkages amongst the microbiota, its impact on gastrointestinal tract and the consequences developed can influence the brain altogether referred to as the microbiota-gut-brain axis and is a is a complex two-way communication. Evidence also supports the genetic basis for the gastrointestinal as well as neurological adverse effects observed in chemotherapy subjects. [23] The close relationship between the CNS as well as the gut microbiota mechanism that allows the microbiota to have a significant impact on the CNS, affecting the behavioural, emotional, and cognitive domains. Numerous possible channels of communication between the microbiota as well as the brain have been identified by experimental evidence. Study reports says that drugs alter the microbial components [24] and the microbial population can also modify the effect of therapeutic agents by altering their metabolism.[25] These include metabolites derived from microbes and their effects on the neurological, hormonal, as well as immune-related signalling pathways that were formerly known as the gut-brain axis.

Chemotherapy led GIT dysbiosis, can exacerbate mucositis by reducing mucosal regeneration, activating toll-like receptor (TLR) signaling pathways and in inflammatory mediators. [26,27] This dysbiosis modifies the alterations in the production of microbial-derived or host derived compounds, including neurotoxic substances, which may contribute to the disruption of blood brain barrier, and also enter the central nervous system directly. The microbiome-gut-brain axis is thought to be important in a few neurocognitive diseases, it has just recently come to light as a possible target for CICI treatment and supportive cancer care due to its possible role in the underlying pathophysiology of the condition. It has been reported that disturbances in the gut microbiome cause anxiety-like behavior and cognitive decline in animals. **[28]** On the other hand, altering their gut flora reduced these actions Furthermore, translational research shows that chemotherapy modifies fecal bacterial populations, a finding supported by human clinical research indicates a close association between gut microbiota and chemobrain and more studies have shown a close relationship between gut microbiota alterations and a variety of neurologic illnesses. [29]

Anxiety, depression, and stress play a significant role in exacerbating chemotherapy-induced cognitive impairment (CICI). These factors if not taken care at right time, can intensify cognitive difficulties including memory loss, attention deficits, and reduced processing speed, by affecting brain function and contributing to neuroinflammation and further intensification of oxidative stress. [30]

Following treatment, many survivors of chemotherapy-induced brain damage report feeling less perceptive and longing for more mental effort to accomplish daily chores. When one returns to the workforce, these challenges become much more significant. While cognitive deficits are commonly observed by therapy, several studies have demonstrated that problems arise primarily when people attempt to return to their usual activities. [31] The majority of research on chemobrain follows patients from the time of diagnosis for up to 18 months following treatment. The self-regulatory model of illness postulates that individuals utilize their conceptions of illness as a scheme to understand their state and manage both immediate and long-term health risks. These are assessed from a range of perspectives including the type, cause, progression, consequences, and severity of cancer as well as dose and extent of therapy. [32] A recent meta-analysis found that perceptions of chronology as chronic, feelings of identity and repercussions, perceived controllability, and reported coherence of the illness were associated with higher levels of distress. [32,33] Furthermore, the research by de Ridder et al found that patients as well as healthcare providers were often unwilling to discuss illness perceptions that went against established assumptions about medicine. On the other hand, consultations that concentrated on how patients saw their illnesses more directly addressed patient concerns and tended to initiate conversations about action planning and their reign in understanding the need to reduce the damage caused by cancer therapy. [34]

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OXIDATIVE STRESS

Another key component involved in CICI is oxidative stress, a process marked by the imbalance between free radicals and antioxidants in the body. When reactive oxygen species (ROS) production and antioxidant availability go out of balance, there will be development of oxidative stress. Central nervous system, because of the higher requirements of oxygen, along with its high lipid contents, is more vulnerable to oxidative stress. Lipid peroxidation mechanisms and structural damage to proteins and DNA are triggered by the escape of reactive oxygen species (ROS) from the defensive mechanisms which leads to their gradual accumulation.

In animal models, anthracyclines effects on oxidative stress seem to be mediated by the generation of inflammatory cytokines. Anthracycline administration, for instance, raises blood TNF-alpha concentrations, which then pass through the blood-brain barrier and cause changes in the brain. This is supported by the fact that anthracyclines have less of an impact on the brains of mice lacking TNF alpha. [35] In another study, Bagnall-Moreau et al. assessed the mRNA expression of the antioxidant as well as oxidative-stress sensitive areas of the hippocampus.[36]

Under normal conditions, Reactive oxygen species are mostly produced in mitochondria, which are important in the production of oxidative stress. Enzymes like catalase, glutathione peroxidase, and superoxide dismutase are part of the mitochondrial antioxidant system, which regulates the homeostasis of reactive oxygen species (ROS) in the mitochondria. Under normal physiological circumstances, mitochondria must effectively modify their morphology in a process known as "mitochondrial dynamics" to continue their roles as well as react to cellular stress. Mitochondrial Fusion and fission are two processes that need to be balanced for dynamics. By permitting the interchange of intact mitochondrial components into damaged mitochondria during stressful situations as a compensatory mechanism, mitochondrial fusion can buffer moderate mitochondrial abnormalities. Conversely, fission has an important role in the segregation as well as removal of damaged mitochondrial components via autophagy and mitophagy which acts like a check to the organelle and maintains its subcellular morphology and integrity. [34,35]

Cancer chemotherapy produces free superoxide radicals in the plasma, which have the potential to oxidize Apolipoprotein A1(ApoA1). In turn, oxidized ApoA1 stimulates the production of TNF alpha, which crosses the blood-brain barrier and causes apoptosis and neuronal death in the brain. [36]

In a prior rat investigation, Dias-Carvalho et al after administering a biweekly injection of 6mg/kg of Mitoxantrone (MTX) to adult male CD-1 mice for three weeks, evaluated the underlying neurotoxic pathways. Oxidative stress, neuronal damage, apoptosis, and autophagy were assessed throughout the brain. Coronal brain sections were used to investigate the hippocampal formation (HF) and the prefrontal cortex (PFC) in greater detail, as these areas have been found to be most affected by "chemobrain." MTX-induced redox imbalance was indicated by increased endothelial nitric oxide synthase, decreased manganese superoxide dismutase production, and a tendency towards a decline in glutathione levels. Moreover, MTX raised the autophagic protein LC3 II, decreased the level of ATP synthase β, and tended to lower the expression of p62. The overall brain showed a decrease in the expression of postsynaptic density protein 95, although the PFC showed hyperphosphorylation of Tau. [37,38] and an increase in the apoptotic marker Bax rose in the PFC as well as the CA3 region. Adult CD-1 mice's brains are harmed by MTX at a cumulative dose that is clinically significant in regions related to memory and cognition. [39] According to some recent trials on cancer patients with paclitaxel, N-acetylcysteine appeared to mitigate oxidative stress and reduced the incidence of peripheral neuropathy. [40,41]

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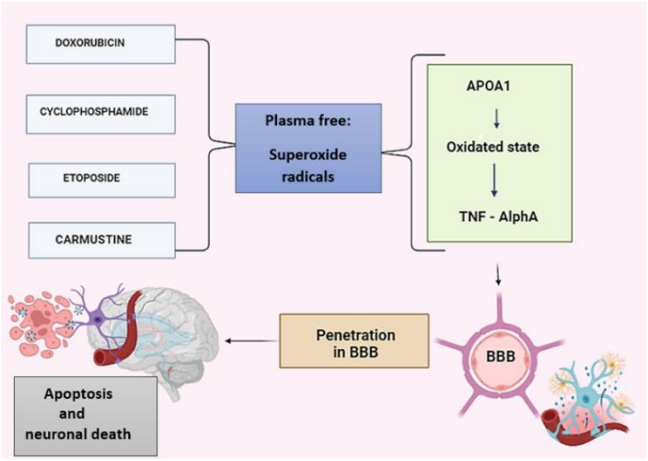

Mechanisms underlying CICI: Involvement of free radicals, BBB and brain changes

Previous research demonstrated that Dox treatment altered the activity of hippocampal Drp-1 and is a sign of increased mitochondrial fission and reflects the disruption of brain mitochondrial dynamics.[42] Additionally, it has been demonstrated that after Dox therapy, the fusion process was enhanced in rats as a compensatory strategy. However, this insufficient protective capacity against the excessive fission process led to brain mitochondrial malfunction as well as cognitive impairment. In the context of several neurodegenerative illnesses, mitochondrial dynamic control has been recognized as a potential therapeutic target. [43] Nevertheless, it is still unclear how mitochondrial dynamic regulation affects chemobrain.

ROLE OF INFLAMMATION

Chemotherapy, via enhanced production/activity of TNF-α, IL-1β, NF-kB, IL-6 and other cytokines along with modulation of several signaling pathways could be the major cause for the development of chemobrain. [44] Patients with cancer have elevated levels of pro-inflammatory cytokines following therapy, which can penetrate the blood-brain barrier, stimulate astrocytes and/or microglia, and enhance the permeability of cytotoxic drugs. [45]

Positron emission tomography (PET) using radiolabeled ligands is specific for the 18kDa translocator protein (TSPO), which is overexpressed in response to neuroinflammation, and it is thought to be a functional marker. [46] In addition to indirect toxicity, cytostatic property of chemotherapeutic agents may also cause direct neuronal damage, decreased neurogenesis and enhanced apoptosis. Neurofilaments, because of their excellent predictive and diagnostic accuracy for diseases like Alzheimer's disease as well as amyotrophic lateral sclerosis, even in their early stages, are promising indicators to study neurotoxicity in humans. [47] Additionally, in patients with breast cancer, neurofilaments rise in a manner that is dependent on the dosage of chemotherapy, indicating that they may be a sign of neuronal damage following chemotherapy. [48]

In-vivo studies on lymphoplasmacytic lymphoma showed an increase in neurotoxicity and neuroplasticity markers and decreased cognitive performance. [49] Further research is required to demark the underlying neuro-restorative and neuro-protective mechanisms of the brain's elevated production of inflammatory cells.

MICROGLIAL CHANGES & NEURONAL PLASTICITY

Microglia are crucial for learning and memory regulation as well as brain homeostasis. Microglia occur to be crucial for experience-driven memory encoding as well as communication with neurons via many signalling pathways, like brain-derived neurotrophic factor. Depletion of brain-derived neurotrophic factor (BDNF) reduces memory capacity. Activated microglia can draw peripheral immune cells to the brain and produce more cytokines, which can impair cognitive function following chemotherapy. Structural examinations following chemotherapy showed reduced gray matter density in brain regions, including the right thalamus, the cerebellum, and the frontal and temporal cortices. [50, 51]

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Chemotherapy may cause a reduction in dendrites and cortical spines, which impairs cortical-based task performance. Lowered focus and processing speed during chemobrain may result from less white matter owing to decreased gliogenesis and changes in neurotransmitter balance, which can be prolongs years after treatment. [52]

Grant, C. V. et al. postulated that chemotherapy activates microglia, which in turn causes cognitive deficits linked to chemotherapy. [53] To confirm this theory, they cured female C57BL/6 mice using a clinically relevant regimen of the popular chemotherapeutic medication paclitaxel. By measuring memory of an unpleasant experience using the contextual fear conditioning (CFC) paradigm, paclitaxel is known to have this effect. When paclitaxel was applied, the percentage area of IBA1 staining in the dentate gyrus of the hippocampal tissue increased therefore, microglia may be crucial to the establishment of chemotherapy-induced neuroinflammation as well as cognitive deficits since PLX5622 markedly decreased hippocampus gene expression of proinflammatory cytokines caused by paclitaxel and improved memory. [54, 55]

Mass spectrometry-based in vitro investigations on PC12 cells have demonstrated that cisplatin may alter the lipids in cell membranes, resulting in aberrant neurotransmitter exocytotic release. The behavioral impairment that has been reported in rats after mithramycin (MTR), may be caused by changes in the dynamics of gene expression. It was discovered that the molecular impacts of MTR were negligible at first and were attributed to many unrelated trajectories. However, after three months, it was revealed the changes in the expression of more than thousand genes changed and were involved in distinct molecular pathways [56]. Whereas, in a rat brain endothelial cell line [RBE4] study, Oxaliplatin caused the breakdown of the tight junctions, which are essential for maintaining the integrity of the blood brain barrier. [57]

By using fast-scan cyclic voltammetry on acute coronal brain slices obtained after death and whole brain preparations from zebrafish, carboplatin inhibits dopamine release and uptake in rats, which may be a cause of mood disorders. Utilizing innovative glutamate-selective microelectrode arrays, doxorubicin acute therapy alters glutamate neurotransmission in the mouse frontal cortex as well as hippocampus. Notably, the dentate gyrus and frontal brain had a 50% delay in glutamate clearance. While molecular processes are not examined, mood alterations were noted in a case-control study including patients with breast cancer. [58]

GENETIC AND EPIGENETIC FACTORS

Research suggests that the control of gene expression through epigenetic mechanisms plays a role in several brain-related illnesses that genetics alone cannot fully account for, including addiction, depression and stress. In addition to the above observations, several researchers have suggested that chemobrain occurs due to epigenetic reasons also. There is a vital role of epigenetics specifically, DNA methylation as well as histone acetylation plays a vital role in neuronal growth and memory. [59]

Epigenetic modifications could be due to environmental stimuli, both internal and external factors along with chemotherapy could be another reason for the development of chemobrain. These changes have the capacity to modify subjective perception and homeostatic function.[60] It can be hypothesized that the common mechanism leading to persistent dyscognition could be epigenetic reprogramming triggered by chemotherapy. [61,62] The role of epigenetic modification in chemobrain appears to be supported by some preliminary data. In an animal model, it was discovered that learning and memory issues were associated with increased histone H3 acetylation and decreased DHAC activity in the hippocampus after CMF therapy. [63,64] The reversal of cytokine-induced DNA methylation occurs two weeks after cytokines are eliminated from the environment, suggesting that chromatin remodeling in the hippocampus could be a possible explanation for the dyscognition during chemo brain. [65-67]

After chemotherapy, each of the components, either separate or in combination, causes alterations in gene expression as well as cell proliferation in the brain, especially in the hippocampus and prefrontal cortical regions. This could ultimately result in the establishment of chronic cognitive impairment. T cells taken from people under psychosocial stress have also been shown

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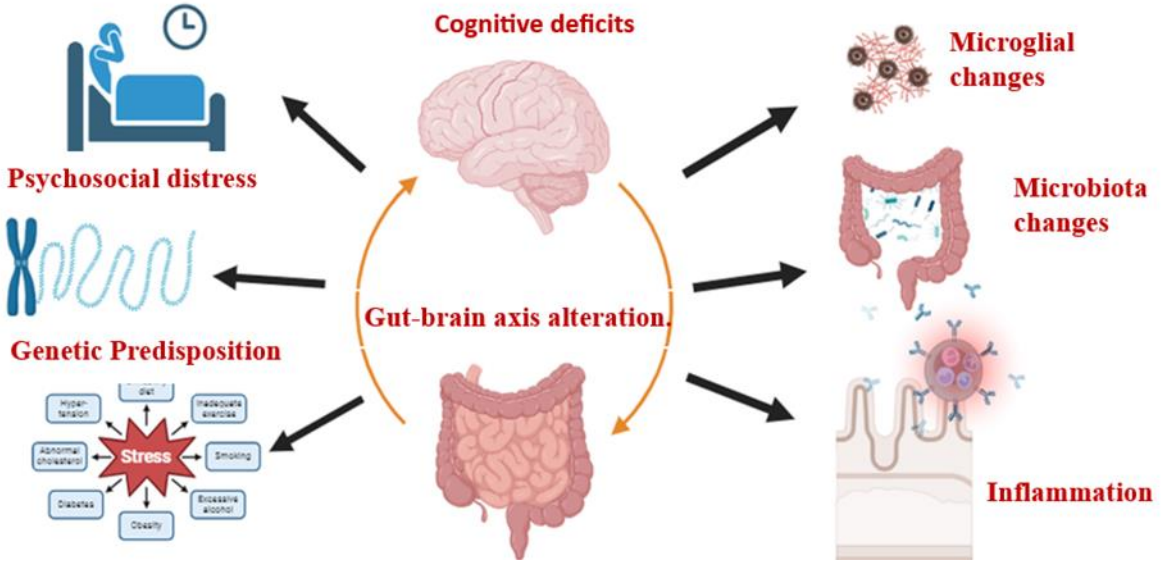
to have acquired changes in their methylation pattern. Recent research in breast cancer patients has demonstrated a link between the emergence and maintenance of cognitive impairments brought on by chemotherapy and epigenetic modifications made after the treatment. In that study, patients who experienced persistent cognitive symptoms were the only ones whose transitory methylation for a selection of genes following treatment persisted. [68,69]

The research outcomes suggest that the infusion of chemotherapeutic medicines starts a chain reaction of biological variations, in cytokines milieu producing enduring epigenetic changes. The subjective experience of cognition is produced by modifications in metabolic activity as well as neuronal transmission that results from these epigenetic variations in gene expression.[70] The discrepancies in neuroimaging results seen among subjects having mild to moderate self-reported cognitive impairment may also be explained by this suggested mechanism. These observations may clarify why chronic cognitive deterioration is a nuanced process. [71,72]

FUTURE MANAGEMENT OF CHEMOBRAIN:

A multi-dimensional approach to chemobrain, may include lifestyle changes, cognitive rehabilitation, psychiatric therapies, and developing medicinal treatments. Therefore, future therapeutic interventions for psychoneurological symptoms brought on by chemotherapy exposure may include acupuncture to tip the balance of pro- as well as anti-inflammatory cytokines, SAM and betaine to alter DNA methylation, sirtuins to alter histone acetylation, or increased brain levels of neurotrophic factors. [73] Memory aides and organizing tools may assist CICI patients to manage daily cognitive issues. [74,75] Research shows that multi-pronged strategy that includes behavioural methods, cognitive training, lifestyle modifications, and novel agents may be helpful for effective chemobrain therapy. Addressing psychological and physiological cognitive impairment may improve quality of life and cognitive outcomes for cancer survivors.[76]



CONCLUSION

Chemobrain, the chemotherapy induced cognitive changes is one of the common and disturbing effects of cancer treatment, affecting a considerable fraction of cancer survivors. It is observed that chemobrain is a result of a several factors comprising of direct neurotoxic effects, inflammation, modification of signal pathway, altered BBB, hormonal changes and genetic inclinations. Consequently, multiple brain regions involved in memory, attention and executive functions are affected. Hence chemobrain can markedly affect daily functioning, work performance, overall quality of life and can endure from months to years. A comprehensive evaluation is essential for better therapy and efficiency. Both objective actions and self-reports are crucial for accurately identifying and managing the chemobrain.

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Cognitive restoration, behavioral therapy and focused interventions are crucial in mitigating chemobrain symptoms. Several therapeutics are being explored but they require more evidence.

References:

1. Ahles, T. A.; Saykin, A. J.; Furstenberg, C. T.; Cole, B.; Mott, L. A.; Titus-Ernstoff, L.; Silberfarb, P. M. Quality of Life of Long-Term Survivors of Breast Cancer and Lymphoma Treated with Standard-Dose Chemotherapy or Local Therapy. J. Clin. Oncol. 2005, 23 [19], 4399–4405
2. DeVita, V. T. The Evolution of Therapeutic Research in Cancer. N. Engl. J. Med. 1978, 298 [16], 907–910.
3. DeVita, V. T.; Chu, E. A History of Cancer Chemotherapy. Cancer Res. 2008, 68 [21], 8643–8653.
4. Craig, T. J.; Abeloff, M. D. Psychiatric Symptomatology among Hospitalized Cancer Patients. Am. J. Psychiatry 1974, 131 [12], 1323–1327.
5. Silberfarb, P. M.; Philibert, D.; Levine, P. M. Psychosocial Aspects of Neoplastic Disease: II. Affective and Cognitive Effects of Chemotherapy in Cancer Patients. Am. J. Psychiatry 1980, 137 [5], 597–601.
6. Schagen, S. B.; van Dam, F. S.; Muller, M. J.; Boogerd, W.; Lindeboom, J.; Bruning, P. Cognitive Deficits after Postoperative Adjuvant Chemotherapy for Breast Carcinoma. Cancer 1999, 85 [3], 640–650.
7. Argyriou, A. A.; Assimakopoulos, K.; Iconomou, G.; Giannakopoulou, F.; Kalofonos, H. P. Either Called "Chemobrain" or "Chemofog," the Long-Term Chemotherapy-Induced Cognitive Decline in Cancer Survivors Is Real. J. Pain Symptom Manage. 2011, 41 [1], 126–139.
8. Wefel, J. S.; Lenzi, R.; Theriault, R. L.; Davis, R. N.; Meyers, C. A. The Cognitive Sequelae of Standard-Dose Adjuvant Chemotherapy in Women with Breast Carcinoma: Results of a Prospective, Randomized, Longitudinal Trial. Cancer 2004, 100 [11], 2292–2299.
9. Freeman, J. R.; Broshek, D. K. Assessing Cognitive Dysfunction in Breast Cancer: What Are the Tools? Clin. Breast Cancer 2002, 3 [Suppl 3], S91–S99.
10. Ahles, T. A.; Saykin, A. Cognitive Effects of Standard-Dose Chemotherapy in Patients with Cancer. Cancer Invest. 2001, 19 [8], 812–820.
11. Hurria, A.; Mohile, S.; Gajra, A.; Klepin, H.; Muss, H.; Chapman, A.; Feng, T.; Smith, D.; Sun, C. L.; De Glas, N.; Cohen, H. J.; Katheria, V.; Doan, C.; Zavala, L.; Levi, A.; Akiba, C.; Tew, W. P. Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults with Cancer. J. Clin. Oncol. 2016, 34 [20], 2366–2371. DOI: 10.1200/JCO.2015.65.4327.
12. Downie, F. P.; Fan, H. M.; Houédé-Tchen, N.; Yi, Q.; Tannock, I. F. Cognitive Function, Fatigue, and Menopausal Symptoms in Breast Cancer Patients Receiving Adjuvant Chemotherapy: Evaluation with Patient Interview after Formal Assessment. Psychooncology 2006, 15, 921–930.
13. Jim, H. S. L.; Phillips, K. M.; Chait, S.; Faul, L. A.; Popa, M. A.; Lee, Y.-H.; Hussin, M. G.; Jacobsen, P. B.; Small, B. J. Meta-Analysis of Cognitive Functioning in Breast Cancer Survivors Previously Treated with Standard-Dose Chemotherapy. J. Clin. Oncol. 2012, 30, 3578–3587.
14. Lu, Y.; Bu, F. Q.; Wang, F.; et al. Recent Advances on the Molecular Mechanisms of Exercise-Induced Improvements of Cognitive Dysfunction. Transl. Neurodegener. 2023, 12 [1], 9.
15. Khosravi, N.; Stoner, L.; Farajivafa, V.; Hanson, E. D. Exercise Training, Circulating Cytokine Levels, and Immune Function in Cancer Survivors: A Meta-Analysis. Brain Behav. Immun. 2019, 81, 92–104.
16. Myers, J. S.; Pathak, H. B.; He, J.; et al. Combined Exercise and Game-Based Cognitive Training Intervention: Correlative Pilot Study of Neurotrophic and Inflammatory Biomarkers for Women with Breast Cancer. Cancer Nurs. 2022, 45 [6], 472–479.
17. Chen, X.; Li, J.; Ren, J.; Hu, X.; Zhu, C.; Tian, Y.; Hu, P.; Ma, H.; Yu, F.; Wang, K. Selective Impairment of Attention Networks in Breast Cancer Patients Receiving Chemotherapy Treatment. Psychooncology 2014, 23, 1165–1171.
18. Brito, M. H. Neurologic Adverse Events of Cancer Immunotherapy. Arq. Neuropsiquiatr. 2022, 80 [5 Suppl 1], 270–280. DOI: 10.1590/0004-282X-ANP-2022-S116.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1716-1727 | ISSN:2251-6727

19. Hurria, A.; Li, D.; Hansen, K.; Patil, S.; Gupta, R.; Nelson, C.; Lichtman, S. M.; Tew, W. P.; Hamlin, P.; Zuckerman, E.; et al. Distress in Older Patients with Cancer. J. Clin. Oncol. 2009, 27, 4346–4351.
20. Ciszkowska-Lyson, B.; Krolicki, L.; Teska, A.; Janowicz-Zebrowska, A.; Krzakowski, M.; Tacikowska, M. Brain Metabolic Disorders after Chemotherapy in the Study by Magnetic Resonance Spectroscopy. Neurol. Neurochir. Pol. 2003, 37 [4], 783–798.
21. Tabaczar, S.; Czepas, J.; Koceva-Chyla, A.; Kilanczyk, E.; Piasecka-Zelga, J.; Gwozdzinski, K. The Effect of the Nitroxide Pirolin on Oxidative Stress Induced by Doxorubicin and Taxanes in the Rat Brain. J. Physiol. Pharmacol. 2017, 68 [2], 295–308.
22. Frontiers in Pharmacology. Chemotherapy-Induced Cognitive Impairment: A Review of the Evidence. Front. Pharmacol. 2023, 14, Article 1251917. DOI: 10.3389/fphar.2023.1251917.
23. Van den Boogaard, W. M.; Komninos, D. S.; Vermeij, W. P. Chemotherapy Side-Effects: Not All DNA Damage Is Equal. Cancers 2022, 14 [3], 627.
24. Maier, L.; Pruteanu, M.; Kuhn, M.; Zeller, G.; Telzerow, A.; Anderson, E. E.; Brochado, A. R.; Fernandez, K. C.; Dose, H.; Mori, H.; Patil, K. R.; Bork, P.; Typas, A. Extensive Impact of Non-Antibiotic Drugs on Human Gut Bacteria. Nature 2018, 555 [7698], 623–628. DOI: 10.1038/nature25979
25. Clarke, G.; Sandhu, K. V.; Griffin, B. T.; Dinan, T. G.; Cryan, J. F.; Hyland, N. P. Gut Reactions: Breaking Down Xenobiotic–Microbiome Interactions. Pharmacol. Rev. 2019, 71 [2], 198–224.
26. Banks, W. A. From Blood-Brain Barrier to Blood-Brain Interface: New Opportunities for CNS Drug Delivery. Nat. Rev. Drug Discov. 2016, 15 [4], 275–292. DOI: 10.1038/nrd.2015.2.
27. Lien, Y. C.; Noel, T.; Liu, H.; Stromberg, A. J.; Chen, K. C.; St Clair, D. K. Phospholipase C-Delta1 Is a Critical Target for Tumor Necrosis Factor Receptor-Mediated Protection Against Adriamycin-Induced Cardiac Injury. Cancer Res. 2006, 66 [8], 4329–4338. DOI: 10.1158/0008-5472.CAN-05-4077.
28. Dinan, T. G.; Cryan, J. F. The Microbiome-Gut-Brain Axis in Health and Disease. Gastroenterol. Clin. North Am. 2017, 46 [1], 77–89. DOI: 10.1016/j.gtc.2016.09.007.
29. Mayer, E. Gut Feelings: The Emerging Biology of Gut–Brain Communication. Nat. Rev. Neurosci. 2011, 12, 453–466. DOI: 10.1038/nrn3039.
30. Long-Smith, C.; O'Riordan, K. J.; Clarke, G.; Stanton, C.; Dinan, T. G.; Cryan, J. F. Microbiota-Gut-Brain Axis: New Therapeutic Opportunities. Annu. Rev. Pharmacol. Toxicol. 2020, 60, 477–502. DOI: 10.1146/annurev-pharmtox-010720-103004.
31. Henderson, F. M.; Cross, A. J.; Baraniak, A. R. "A New Normal with Chemobrain": Experiences of the Impact of Chemotherapy-Related Cognitive Deficits in Long-Term Breast Cancer Survivors. Health Psychol. Open 2019, 6 [1], 2055102919832234. DOI: 10.1177/2055102919832234
32. Siegel, R. L.; Miller, K. D.; Jemal, A. Cancer Statistics, 2020. CA Cancer J. Clin. 2020, 70, 7–30. DOI: 10.3322/caac.21590.
33. Subramaniam, B.; Bowen, J. M. The Microbiota-Gut-Brain Axis: An Emerging Therapeutic Target in Chemotherapy-Induced Cognitive Impairment. Neurosci. Biobehav. Rev. 2020, 116, 470–479. DOI: 10.1016/j.neubiorev.2020.07.023.
34. Jordan, K. R.; Loman, B. R.; Bailey, M. T.; Pyter, L. M. Gut Microbiota-Immune-Brain Interactions in Chemotherapy-Associated Behavioral Comorbidities. Cancer 2018, 124 [20], 3990–3999. DOI: 10.1002/cncr.31533.
35. De Ridder, D. T. D.; Theunissen, N. C.; van Dulmen, S. M. Does Training General Practitioners to Elicit Patient's Illness Representations and Action Plans Influence Their Communication as a Whole? Patient Educ. Counsel. 2007, 66, 327–336. DOI: 10.1016/j.pec.2006.10.004.
36. Henderson, F. M.; Cross, A. J.; Baraniak, A. R. "A New Normal with Chemobrain": Experiences of the Impact of Chemotherapy-Related Cognitive Deficits in Long-Term Breast Cancer Survivors. Health Psychol. Open 2019, 6 [1], 2055102919832234. DOI: 10.1177/2055102919832234.
37. Bagnall-Moreau, C.; Chaudhry, S.; Salas-Ramirez, K.; Ahles, T.; Hubbard, K. Chemotherapy-Induced Cognitive Impairment Is Associated with Increased Inflammation and Oxidative Damage in the

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1716-1727 | ISSN:2251-6727

Hippocampus. Mol. Neurobiol. 2019, 56, 7159–7172. DOI: 10.1007/s12035-019-1486-6.

38. Bano, N.; Najam, R. Histopathological and Biochemical Assessment of Liver Damage in Albino Wistar Rats Treated with Cytotoxic Platinum Compounds in Combination with 5-Fluorouracil. Arch. Med. Sci. 2019, 15 [4], 1092–1103. DOI: 10.5114/aoms.2019.86064.
39. Ren, X.; Keeney, J. T. R.; Miriyala, S.; Noel, T.; Powell, D. K.; Chaiswing, L.; Bondada, S.; St. Clair, D. K.; Butterfield, D. A. The Triangle of Death of Neurons: Oxidative Damage, Mitochondrial Dysfunction, and Loss of Choline-Containing Biomolecules in Brains of Mice Treated with Doxorubicin. Advanced Insights into Mechanisms of Chemotherapy-Induced Cognitive Impairment ["Chemobrain"]. Free Radic. Biol. Med. 2019, 134, 1–8. DOI: 10.1016/j.freeradbiomed.2019.01.017.
40. Gaman, A. M.; Uzoni, A.; Popa-Wagner, A.; Andrei, A.; Petcu, E. B. The Role of Oxidative Stress in Etiopathogenesis of Chemotherapy-Induced Cognitive Impairment ["Chemobrain"]. Aging Dis. 2016, 7 [3], 307–317. DOI: 10.14336/AD.2015.0811.
41. Dias-Carvalho, A.; Ferreira, M.; Reis-Mendes, A.; Ferreira, R.; Bastos, M. L.; Fernandes, E.; Sá, S. I.; Capela, J. P.; Carvalho, F.; Costa, V. M. Chemobrain: Mitoxantrone-Induced Oxidative Stress, Apoptotic and Autophagic Neuronal Death in Adult CD-1 Mice. Arch. Toxicol. 2022, 96 [6], 1767–1782. DOI: 10.1007/s00204-022-03143-0.
42. Khalefa, H. G.; Shawki, M. A.; Aboelhassan, R.; El Wakeel, L. M. Evaluation of the Effect of N-Acetylcysteine on the Prevention and Amelioration of Paclitaxel-Induced Peripheral Neuropathy in Breast Cancer Patients: A Randomized Controlled Study. Breast Cancer Res. Treat. 2020, 183, 117–125. DOI: 10.1007/s10549-019-05223-x.
43. Hara, Y.; McKeehan, N.; Dacks, P. A.; Fillit, H. M. Evaluation of the Neuroprotective Potential of N-Acetylcysteine for Prevention and Treatment of Cognitive Aging and Dementia. J. Prev. Alzheimer's Dis. 2017, 4, 201–206. DOI: 10.14283/jpad.2017.13.
44. Katz, M.; Won, S. J.; Park, Y.; Orr, A.; Jones, D. P.; Swanson, R. A.; Glass, G. A. Cerebrospinal Fluid Concentrations of N-Acetylcysteine After Oral Administration in Parkinson's Disease. Park. Relat. Disord. 2015, 21, 500–503. DOI: 10.1016/j.parkreldis.2015.01.007.
45. Griñan-Lison, C.; Blaya-Cánovas, J. L.; López-Tejada, A.; Ávalos-Moreno, M.; Navarro-Ocón, A.; Cara, F. E.; Granados-Principal, S. Antioxidants for the Treatment of Breast Cancer: Are We There Yet? Antioxidants 2021, 10 [2], 205. DOI: 10.3390/antiox10020205.
46. Allen, B. D.; Apodaca, L. A.; Syage, A. R.; Markarian, M.; Baddour, A. A. D.; Minasyan, H.; et al. Attenuation of Neuroinflammation Reverses Adriamycin-Induced Cognitive Impairments. Acta Neuropathol. Commun. 2019, 7, 186. DOI: 10.1186/s40478-019-0785-2.
47. DuBoff, B.; Feany, M.; Götz, J. Why Size Matters – Balancing Mitochondrial Dynamics in Alzheimer's Disease. Trends Neurosci. 2013, 36, 325–335. DOI: 10.1016/j.tins.2013.02.007.
48. Burté, F.; Carelli, V.; Chinnery, P. F.; Yu-Wai-Man, P. Disturbed Mitochondrial Dynamics and Neurodegenerative Disorders. Nat. Rev. Neurol. 2015, 11, 11–24. DOI: 10.1038/nrneurol.2014.271.
49. Cauli, O. Oxidative Stress and Cognitive Alterations Induced by Cancer Chemotherapy Drugs: A Scoping Review. Antioxidants 2021, 10 [7], 1116. DOI: 10.3390/antiox10071116.
50. Janelsins, M. C.; Kesler, S. R.; Ahles, T. A.; Morrow, G. R. Prevalence, Mechanisms, and Management of Cancer-Related Cognitive Impairment. Int. Rev. Psychiatry 2014, 26 [1], 102–113. DOI: 10.3109/09540261.2013.842663.
51. Ongnok, B.; Maneechote, C.; Chunchai, T.; Pantiya, P.; Arunsak, B.; Nawara, W.; Chattipakorn, N.; Chattipakorn, S. C. Modulation of Mitochondrial Dynamics Rescues Cognitive Function in Rats with 'Doxorubicin-Induced Chemobrain' via Mitigation of Mitochondrial Dysfunction and Neuroinflammation. FEBS J. 2022, 289 [20], 6435–6455. DOI: 10.1111/febs.16409
52. Sahu, K.; Langeh, U.; Singh, C.; Singh, A. Crosstalk between Anticancer Drugs and Mitochondrial Functions. Curr. Res. Pharmacol. Drug Discov. 2021, 2, 100047. DOI: 10.1016/j.crphar.2021.100047.
53. Koppelmans, V.; Breteler, M. M.; Boogerd, W.; Seynaeve, C.; Gundy, C.; Schagen, S. B.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1716-1727 | ISSN:2251-6727

Neuropsychological Performance in Survivors of Breast Cancer More than 20 Years after Adjuvant Chemotherapy. J. Clin. Oncol. 2012, 30, 1080–1086. DOI: 10.1200/JCO.2011.36.1637.

54. Van Schaik, T. A.; Chen, K. S.; Shah, K. Therapy-Induced Tumor Cell Death: Friend or Foe of Immunotherapy? Front. Oncol. 2021, 11, 678562. DOI: 10.3389/fonc.2021.678562.
55. Pan, S. T.; Li, Z. L.; He, Z. X.; Qiu, J. X.; Zhou, S. F. Molecular Mechanisms for Tumor Resistance to Chemotherapy. Clin. Exp. Pharmacol. Physiol. 2016, 43, 723–737. DOI: 10.1111/1440-1681.12582.
56. Seitz, S. J.; Schleithoff, E. S.; Koch, A.; Schuster, A.; Teufel, A.; Staib, F.; Stremmel, W.; Melino, G.; Krammer, P. H.; Schilling, T.; et al. Chemotherapy-Induced Apoptosis in Hepatocellular Carcinoma Involves the p53 Family and Is Mediated via the Extrinsic and the Intrinsic Pathway. Int. J. Cancer 2010, 126, 2049–2066. DOI: 10.1002/ijc.24845
57. Grant, C. V.; Sullivan, K. A.; Wentworth, K. M.; Otto, L. D.; Strehle, L. D.; Otero, J. J.; Pyter, L. M. Microglia Are Implicated in the Development of Paclitaxel Chemotherapy-Associated Cognitive Impairment in Female Mice. Brain Behav. Immun. 2023, 108, 221–232. DOI: 10.1016/j.bbi.2022.08.003.
58. Notter, T.; Coughlin, J. M.; Sawa, A.; Meyer, U. Reconceptualization of Translocator Protein as a Biomarker of Neuroinflammation in Psychiatry. Mol. Psychiatry 2018, 23, 36–47. DOI: 10.1038/mp.2017.125.
59. De Vocht, J.; Blommaert, J.; Devrome, M.; Radwan, A.; Van Weehaeghe, D.; De Schaepdryver, M.; Ceccarini, J.; Rezaei, A.; Schramm, G.; Van Aalst, J.; et al. Use of Multimodal Imaging and Clinical Biomarkers in Presymptomatic Carriers of C9orf72 Repeat Expansion. JAMA Neurol. 2020, 77, 1008–1017. DOI: 10.1001/jamaneurol.2020.0246.
60. Wefel, J. S.; Schagen, S. B. Chemotherapy-Related Cognitive Dysfunction. Curr. Neurol. Neurosci. Rep. 2012, 12, 267–275. DOI: 10.1007/s11910-012-0286-0.
61. Winocur, G.; Binns, M. A.; Tannock, I. Donepezil Reduces Cognitive Impairment Associated with Anti-Cancer Drugs in a Mouse Model. Neuropharmacology 2011, 61, 1222–1228. DOI: 10.1016/j.neuropharm.2011.07.010
62. Grant, C. V.; Sullivan, K. A.; Wentworth, K. M.; Otto, L. D.; Strehle, L. D.; Otero, J. J.; Pyter, L. M. Microglia Are Implicated in the Development of Paclitaxel Chemotherapy-Associated Cognitive Impairment in Female Mice. Brain Behav. Immun. 2023, 108, 221–232. DOI: 10.1016/j.bbi.2022.12.004.
63. Winocur, G. Chemotherapy and Cognitive Impairment: An Animal Model Approach. Can. J. Exp. Psychol. 2017, 71 [4], 265–273. DOI: 10.1037/cep0000105.
64. Horowitz, T. S.; Suls, J.; Trevino, M. A Call for a Neuroscience Approach to Cancer-Related Cognitive Impairment. Trends Neurosci. 2018, 41 [8], 493–496. DOI: 10.1016/j.tins.2018.05.005.
65. Lacourt, T. E.; Heijnen, C. J. Mechanisms of Neurotoxic Symptoms as a Result of Breast Cancer and Its Treatment: Considerations on the Contribution of Stress, Inflammation, and Cellular Bioenergetics. Curr. Breast Cancer Rep. 2017, 9 [2], 70–81. DOI: 10.1007/s12609-017-0245-0.
66. Mohammadi, A. S.; Li, X.; Ewing, A. G. Mass Spectrometry Imaging Suggests That Cisplatin Affects Exocytotic Release by Alteration of Cell Membrane Lipids. Anal. Chem. 2018, 90 [14], 8509–8516.
67. Asor, E.; Ben-Shachar, D. Gene Expression Dynamics Following Mithramycin Treatment: A Possible Model for Post-Chemotherapy Cognitive Impairment. Clin. Exp. Pharmacol. Physiol. 2018, 45 [10], 1028–1037.
68. Kaplan, S. V.; Limbocker, R. A.; Gehringer, R. C.; et al. Impaired Brain Dopamine and Serotonin Release and Uptake in Wistar Rats Following Treatment with Carboplatin. ACS Chem. Neurosci. 2016, 7 [6], 689–699.
69. Field T. M.; Shin, M.; Stucky, C. S.; et al. Electrochemical Measurement of Dopamine Release and Uptake in Zebrafish Following Treatment with Carboplatin. ChemPhysChem 2018, 19 [10], 1192–1196.
70. Wang, X. M.; Walitt, B.; Saligan, L.; Tiwari, A. F.; Cheung, C. W.; Zhang, Z. J. Chemobrain: A Critical Review and Causal Hypothesis of Link between Cytokines and Epigenetic Reprogramming

Associated with Chemotherapy. Cytokine 2015, 72 [1], 86–96.

71. Mantovani, A.; Pierotti, M. A. Cancer and Inflammation: A Complex Relationship. Cancer Lett. 2008, 267 [2], 180–181.
72. Trask, P. C.; et al. Psychiatric Side Effects of Interferon Therapy: Prevalence, Proposed Mechanisms, and Future Directions. J. Clin. Oncol. 2000, 18 [11], 2316–2326. DOI: 10.1200/JCO.2000.18.11.2316.
73. Branca, J. J. V.; Maresca, M.; Morucci, G.; et al. Oxaliplatin-Induced Blood Brain Barrier Loosening: A New Point of View on Chemotherapy-Induced Neurotoxicity. Oncotarget 2018, 9 [34], 23426–23438. DOI: 10.18632/oncotarget.25647.
74. Glaser, R.; Kiecolt-Glaser, J. K. Stress-Induced Immune Dysfunction: Implications for Health. Nat. Rev. Immunol. 2005, 5 [3], 243–251.
75. Gibb, J.; Al-Yawer, F.; Anisman, H. Synergistic and Antagonistic Actions of Acute or Chronic Social Stressors and an Endotoxin Challenge Vary over Time Following the Challenge. Brain Behav. Immun. 2013, 28, 149–158. DOI: 10.1016/j.bbi.2012.09.005.
76. Mao, X.; Wu, S.; Huang, D.; Li, C. Complications and Comorbidities Associated with Antineoplastic Chemotherapy: Rethinking Drug Design and Delivery for Anticancer Therapy. Acta Pharm. Sin. B 2024. DOI: 10.1016/j.apb.2023.12.003.