

The Mechanism of Chemotherapy Toxicity to the Hippocampus and its Intervention Measures

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Abstract. This article explores the comprehensive recovery strategies necessary for individuals following chemotherapy, focusing on a holistic approach that includes medications, lifestyle changes, and environmental interventions. The initial section delves into the importance of personalized medical interventions such as targeted therapies, immunotherapy and hormonal treatments, highlighting their critical role in effectively controlling cancer while minimizing side effects. Detailed focus on the mechanisms of adverse effects, particularly the neurotoxic effects of chemotherapy drugs on the hippocampus, elucidates the biological basis of chemotherapy-induced cognitive impairment (often referred to as "chemo brain"). Environmental interventions are another core component of recovery strategies focused on reducing toxin exposure and creating therapeutic spaces conducive to recovery. Provides practical advice for achieving a healthier living environment, including choosing organic foods, using natural household products, and improving indoor air quality. The findings presented here provide a fundamental understanding of brain structural changes following chemotherapy, providing insights into potential mitigation strategies for cognitive recovery.

Keywords: Chemotherapy toxicity, hippocampus, intervention measures.

1. Introduction

Chemotherapy is the core method of modern cancer and has achieved remarkable results in prolonging patients' lives. Chemotherapy, while keeping cancer patients alive, also brings some negative effects to people's brains.

The side effects of chemotherapy have attracted more and more attention from medical scholars and patients, especially the effects of chemotherapy on cognitive function. In children and adults treated with chemotherapy, there are many reports of neurotoxic adverse effects, such as memory disruption and impaired attention. In addition, the symptoms of these patients will become more and more severe after stopping chemotherapy treatment, and may be severely impaired and unable to return to the previous level of performance, which will greatly affect the quality of life of patients. Almost all types of chemotherapy drugs have adverse effects on the nervous system, and the hippocampus is known to regulate emotions and maintain memory, among other functions. As a result, many chemotherapy drugs are thought to potentially disrupt the function of the hippocampus and make it damaged [1]. The cognitive impairment that occurs in cancer patients after chemotherapy is also referred to as "chemo brain", specifically cognitive impairment and memory loss related to hippocampal function. To investigate the mechanism, the researchers increased their research, using neuroimaging tests to find neurological disruption, including abnormalities in the white matter of the patients' brains. Common chemotherapy drugs can induce changes in total brain volume after treatment, including persistent changes in white and gray matter. Chemotherapy-related changes in white matter integrity were observed in the prefrontal cortex and temporal lobes, which are responsible for mediating executive function and memory processing, and the severity of the damage increased with the dose. The volume of the midbrain temporal lobe and hippocampus also decreases. Clinical studies of the effects of chemotherapy drugs on rats and mice have observed several common cognitive impairments in patients, including hippocampal-mediated memory impairments and deficits in working memory [2]. Although there are few studies in this area at present, and the research on chemotherapy-induced cognitive impairment is still in the exploratory stage, there is still a lack of

adequate understanding of cognitive impairment in cancer patients [3]. But these studies do show that chemotherapy drugs have an impact on cognitive impairment in cancer survivors. In order to help these cancer survivors avoid cognitive impairment, chemotherapy drugs damage the hippocampus caused by cognitive impairment, improve their standard of living and quality of life.

This paper will study the mechanism of cognitive dysfunction caused by the damage of chemotherapy drugs to the hippocampus, and further explore and explain the mechanism. This article aims to provide a comprehensive reference for future development and research of more effective interventions to reduce or prevent cognitive impairment caused by chemotherapy drugs.

2. The mechanism of chemotherapy-induced hippocampal toxicity

2.1. Hippocampal toxicity

There are a number of mechanisms that can lead to hippocampal toxicity after chemotherapy, such as hippocampal somatic cell damage and neuroinflammatory response. The hippocampus is particularly vulnerable to damage caused by chemotherapy drugs, and the volume of the hippocampus decreases after chemotherapy, which can be attributed to some pathological physiological changes. The researchers observed differences in the morphology of neurons in the hippocampus in response to several classes of chemotherapy drugs. As shown in figure 1, adult hippocampal neurogenesis is the continuous addition of new neurons to the hippocampus during adulthood.

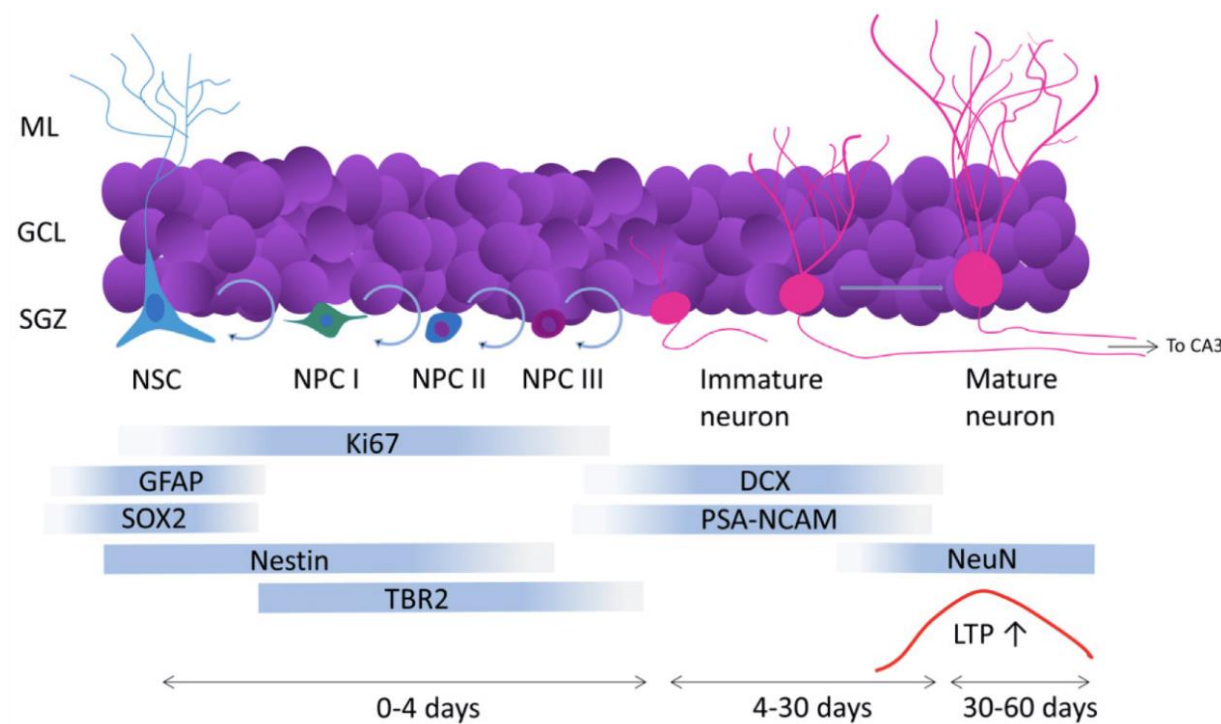


Fig 1. The adult hippocampal neurogenesis process [2].

2.2. 5-fluorouracil (5-FU)

5-FU has been found to have an impact on the mitotic process in the brain. In an experiment using mice, the mice in the experimental group were treated with 40 mg/kg of 5-FU for 6 months, with three 5-day treatment courses. The results showed that this treatment method caused damage to the mice's neurons compared to the control group. Interestingly, there was no significant difference in the short-term damage between BRDU-labeled cells and the control group. It was only after long-term use that the damaging effect of 5-FU on hippocampal cells became evident. This suggests that neurons that are normally long-lived may be affected by the treatment. Another study using mice adjusted the dosage to 25 mg/kg of 5-FU and observed a significant inhibitory effect on BRDU+ cells

after a 2-week treatment cycle. Several weeks after the treatment, the number of Ki-67 and DCX-expressing cells continued to decrease, indicating long-term inhibition of cell proliferation. This inhibition also affected the rats' memory for the novel object location task and spatial memory. Additionally, the number of P21-expressing cells in the SGZ was reduced four days and one month after the end of 5-FU treatment, indicating disruption of early and sustained cell division activity and apoptosis. Overall, these findings suggest that 5-FU can cause damage to the hippocampus and affect its memory function [2].

2.3. Cytarabine (Ara-C)

Ara-C, a cysteine analog, is commonly used to treat leukemia and breast cancer by blocking DNA and RNA replication. In a study on mice, they were injected with cytarabine at a dose of 250 mg/kg three times within five days. The researchers evaluated cell proliferation in the hippocampus immediately after injection and up to 56 days later to understand the short-term and long-term cytotoxic effects of cytarabine. They found that hippocampal cell proliferation decreased over time, with the most significant decrease observed two months after treatment. However, no significant effects were observed after one week of treatment. Additionally, TUNEL staining revealed higher levels of apoptotic cells in the hippocampus within two weeks after treatment, which returned to levels similar to the control group after 56 days. This pattern suggests that hippocampal cells may retain some ability to divide actively after cytarabine treatment. However, increased apoptosis rates led to early hippocampal failure and neuronal structural instability. Over time, as cell death rates normalized, defects in hippocampal neuron population renewal may reduce the plasticity of the hippocampal neural network, impacting learning and memory functions [2].

2.4. Doxorubicin

AC chemotherapy mainly refers to the dual drug combination chemotherapy regimen consisting of anthracycline doxorubicin (DOX) and cyclophosphamide. AC chemotherapy can lead to an increase in pro-inflammatory cytokines, which then leads to an increase in inflammation. The expression of inflammatory proteins indicated that oxidative damage may have occurred with AC chemotherapeutic drugs [4]. DOX is an anthracycline that disrupts the production of RNA by inserting DNA, and it is also a common antitumor drug [2,5]. Some researchers have observed that behavioral changes in rodents given adriamycin alone are associated with the production of pro-inflammatory cytokines and enhanced oxidative damage in plasma and brain [4]. Subsequent studies demonstrated that DOX has an indirect central nervous system toxic effect as a result of TNF- α penetrating the blood-brain barrier. This is due to the oxidation of APOA1 by DOX, which in turn stimulates macrophages to produce TNF- α (tumor necrosis factor α), resulting in large quantities of plasma TNF- α . Tnf- α can promote direct oxidative damage to the central nervous system, resulting in neuronal damage [5]. Although a single dose of DOX does not produce long-term neurotoxic effects on proliferating hippocampal cells, the combination of DOX and CPP can disrupt hippocampal neurogenesis [2].

The above are the three mechanisms by which chemotherapy damages the hippocampus. 5-fluorouracil and cytarabine cause death or apoptosis of hippocampal cells by destroying them. This can damage the hippocampus and affect its functions such as memory and learning. DOX, on the other hand, causes oxidative damage to the brain, and when it is used in combination with CPP, it causes damage to the hippocampus.

3. Medical Interventions

3.1. Targeted Therapy

For patients undergoing targeted therapy as part of their post-chemotherapy treatment, monitoring and managing side effects is crucial. For example, patients on EGFR inhibitors might experience skin rash as a common side effect. A dermatology consultation before starting treatment can provide

preemptive skincare strategies. Use of gentle, non-irritating skin care products, and avoiding direct sun exposure by wearing protective clothing and using broad-spectrum sunscreens, can mitigate these effects. Regular follow-up appointments allow for adjustments to the treatment plan as needed, ensuring the therapy's effectiveness while minimizing discomfort [6].

3.2. Immunotherapy

Immunotherapy's immune-boosting properties can sometimes lead to the immune system attacking normal organs, a condition known as immune-related adverse events (irAEs). These can range from mild to severe and might affect the skin, gastrointestinal tract, liver, endocrine glands, and other organs [7]. Close monitoring for symptoms like diarrhea, skin rash, fatigue, or any new or unusual symptoms is essential. Early intervention with steroids or other immunosuppressive medications can effectively manage irAEs, allowing patients to continue benefiting from immunotherapy. Patient education on symptom awareness and prompt reporting is key to managing these side effects effectively.

3.3. Hormonal Therapy

For patients on hormonal therapy, such as those with breast or prostate cancer, managing side effects like hot flashes, mood swings, and changes in sexual function is important for quality of life. Lifestyle modifications, such as wearing light clothing, using cooling gels or fans, and avoiding triggers like hot drinks, can alleviate hot flashes. For mood swings, strategies like regular physical activity, adequate sleep, and stress management techniques such as deep breathing exercises and mindfulness can be beneficial. Discussing sexual health openly with healthcare providers can lead to effective management strategies, including medications or counseling for sexual dysfunction [8].

3.4. Mental Health

For deeper mental health support post-chemotherapy, exploring options like cognitive-behavioral therapy (CBT) with a therapist experienced in oncology can be particularly beneficial. CBT can help patients develop coping strategies for dealing with anxiety and depression by identifying and challenging negative thought patterns [9]. Additionally, joining a support group specifically for cancer survivors can provide a sense of community and mutual support, offering a space to share experiences and coping strategies. For those experiencing significant emotional distress, medications such as antidepressants or anti-anxiety drugs may be necessary, under the guidance of a psychiatrist or a physician [10].

4. Conclusion

In conclusion, this paper has comprehensively examined the multifaceted approach required for effective recovery following chemotherapy, emphasizing a holistic strategy that encompasses medical interventions, lifestyle modifications, and environmental adjustments. Central to our discussion was the exploration of personalized medical treatments such as targeted therapy, immunotherapy, and hormonal therapy, which are instrumental in addressing the specific needs of cancer survivors while minimizing adverse effects. Importantly, we delved into the neurotoxic effects of chemotherapy on the hippocampus, offering insight into the mechanisms underlying chemotherapy-induced cognitive impairments, or "chemo brain," and highlighting the necessity for research and interventions aimed at mitigating these impacts.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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