Review Article

Chemotherapy induced central nervous system toxicity and syndromes

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ABSTRACT

Chemotherapy is used for the treatment of cancer but major drawback is central nervous system (CNS) toxicity (Hippocampus and cortical toxicity). Cancer patient's shows less sensitivity and tolerance on the usage of chemotherapy that causes damages in the body mainly it affects the targets (hippocampus and cortical regions) of the CNS. CNS toxicity occurs through microglia activation, apoptotic cell death, neuronal demyelination, and oxidative stress. In this article, we have discussed the chemotherapy induced cortical toxicity, hippocampus toxicity, and syndromes of the CNS. It causes toxic effect either single drug or combination of more than one drug.

Keywords: Central nervous system syndromes, chemotherapy, cortical toxicity, hippocampus toxicity

INTRODUCTION

Chemotherapy is the group of drugs used for the treatment of cancer. It is used as an optic approach for the treatment of various types of tumor. Cancer patients show less sensitivity and tolerance with the use of complex doses of chemotherapy. The long-term use of combination therapy of antineoplastic agents produces adverse drug reactions (ADRs) on their use such as hippocampus toxicity, cortical toxicity, organ toxicity, and extrapyramidal symptoms. Recent studies reported that developed countries are more prone to get ADRs as compared to developing countries.[1,2] Anti–cancer drugs affects the immune system and that is why the immune system is compromised in patients are more prone to get toxicity. Chemotherapy stimulates the release of pro-inflammatory agents such as interleukin (IL)-6, IL-β, and tumor necrosis factor alpha (TNF-α) with the activation of macrophages, T-cells, monocytes leads to cell death. It occurs in conditions like intracranial metastasis (granulomatous situations and focal demyelination),[3] by drugs inducing seizures (cisplatin and busulfan), and Para-neoplastic syndromes (PNS) (hippocampus and temporal lobe are involved in this).[4] Seizures show direct and indirect changes with the use of chemotherapy (e.g., cisplatin metabolic changes such as renal toxicity).[5] Methylene blue is used in case of ifosfamide induced central nervous system (CNS) toxicity.[6,7] Stimulants like high-dose of fluorouracil are also found to cause nervous syndromes PNS.[8]

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CHEMOTHERAPY ROLE IN HIPPOCAMPUS TOXICITY

Hippocampus is situated below the cerebral cortex in the centered temporal lobe of the human brain. Hippocampus controls the functions such as short term-memory, navigation activity, and emotional responses. New neurons are generated in dentate gyrus of the hippocampus and receive information from the hippocampus.[9] Memory impairment occurs by mechanisms such as telomere shortening, altered hormonal levels, neuron related polymorphism in neurons, oxidative stress, blood–brain barrier (BBB) disruption, and cytokine dysregulation.[10] Hippocampus toxicity occurs through rise in extracellular level of glutamate and leads to glutamate excitotoxicity. It also raises the level of oxidative stress in brain hippocampus region and further failure leads to memory impairment. Mitomycin-c is an antineoplastic antibiotics drug that alkylates the deoxyribonucleic acid (DNA) sequence, beaks

the strands of DNA, and inhibits the process of synthesis of DNA. 5-Fluorouracil induces the apoptosis in brain and suppression or proliferations of neuron in dentate gyrus of the hippocampus. The disturbance of dentate gyrus input the signals from dentate gyrus to Cornu Ammonis (CA)3 which sends signals to CA1 is disturbed and leads to hippocampus neurodegeneration degenerations. It causes functional impairment in the hippocampus.[11] Recent reports, it was found that about 10–80% of patients receiving chemotherapy (in breast cancer) has chances of memory impairment.[12] Tamoxifen has found to deficits the visual and verbal related memory problems.[13] It crosses BBB disruption with induction of oxidative stress (imbalance in reactive oxygen species [ROS] and apolipoprotein A1) that also causes mutations in toll-like receptor, multi drug resistance, and multidrug resistance associated proteins. Oxidative stress induces cytokine dysregulation with disruption in TNF-α and IL-1β expressions. Methotrexate activates the microglia that is responsible for the blocking of proliferations, blocks the complete differentiations, after the microglia activation it activates ROS which interrupts the synaptic plasticity which leads to neuronal toxicity [Figure 1]. It results in mutations in viability of neurons, which reduces the antioxidant defense that leads to fragile ROS balance. It increases the counts of the ROS which is triggers the oxidative stress that is responsible for the shifting of positive modulation of synaptic plasticity and memory which leads to impairment. These changes are responsible for the impairment of the memory.[14] Temozolomide is used for cancer with the DNA linking properties, which are shown to cause impairment in hippocampus neurogenesis process and disturbs the hippocampus theta band oscillations in rodents' models. A theta band frequency represents the short-term memory, long-term memory, and spatial memory. This drug does not impair the long-term memory but it only impairs the short-term memory problems on the usage of chemotherapy. Three targets are responsible to induce hippocampus toxicity: (1) Activation of oxidative stress causes myelin toxicity, (2) direct cellular toxicity or inflammation and oxidative stress impaired hippocampal neurogenesis that lead to toxicity of hippocampus, and (3) inflammation induces neurovascular damage and it also impairs the hippocampus neurogenesis. All three above points cause neurocognitive dysfunction. Methotrexate induces inflammatory responses which was seen in methotrexate treated mice and shown in an increase of microglia and activation of cyclooxygenase-2 which leads to induction of nitric oxide synthase levels to cause inflammatory responses to impairs hippocampus that alters the learning and memory problems.[15] Studies found that administration of alkylating agents such as Oxaliplatins attach with the DNA strands and produces mutations that leads to apoptotic cell death through passing through BBB to cerebrospinal fluid (CSF) and extracellular fluids in regions of the brain to causes hippocampus damage that leads to cognitive impairment.[16]

CHEMOTHERAPY CAUSES CORTICAL TOXICITY

Human brain is the consisted of billions of neurons which communicate through various connections and synapses. Frontal

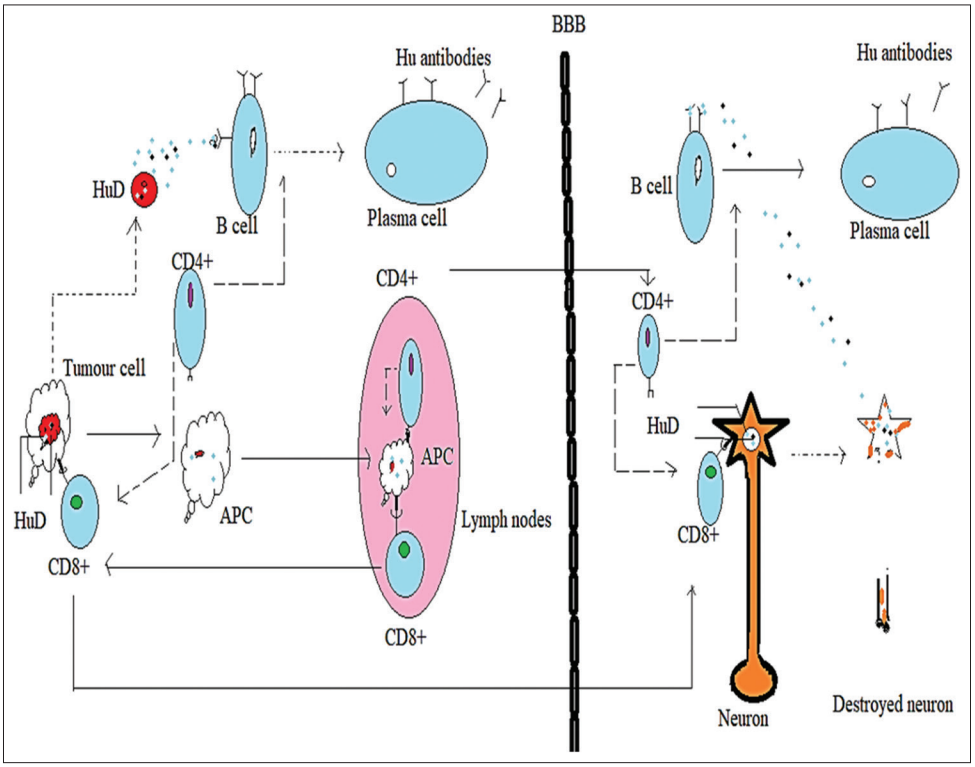

Figure 1: Pathogenesis of para neoplastic syndromes associated with antibodies

Line demonstrations	Abbreviations
Differentiation process	APC-Antigen Presenting Cell
Transport process	CD-Cluster of Differentiations
Stimulation process	BBB-Blood Brain barrier

lobe is located in frontal region of cerebral hemisphere control the various functions like (speech, language, social behavior, and decision-making) and parietal lobes are located posterior to the frontal lobe and on superior side of temporal lobe that controls functions such as spatial recognition, language, and stereo gnosis and temporal lobes are found in posterior to frontal lobe and inferior to parietal lobe that controls the functions such as recognizing memory recollection and familiarity, sound recognition through subjects and vision, and last lobe is occipital lobe is smallest lobe and is found in posterior region of the frontal and parietal lobe that controls the functions such as processing and interpretation of the vision.[17] Chemotherapy causes cortical toxicity by disrupting or damaging these lobes. Cyclosporin-A and FK-506 (immunosuppressant) with chemotherapy (busulfan) are found to cause the neurotoxicity. It causes the lesion which transfer or modify the lesion from white matter to a mixed cortical and white matter pattern. It causes apoptotic cell death through release of cytochrome-C that leads to activation of pre and pro apoptotic agents for the induction of caspases for apoptosis process. At various doses of cyclosporine-A cause problems such as seizures (301–1360 ug/L dose at different days), and confusions (170–440 ug/L dose), headache (140 ug/L).[18] Ara-c causes cerebral dysfunctions. Methotrexate and etoposide induce seizures and cerebral interactions.

SYNDROMES CAUSED BY CHEMOTHERAPY

Syndromes are the diseases which occurred by specific genes. Chemotherapy (cisplatin, corticosteroids, nelarabine, and cytarabine) induces various syndromes in the CNS such as neurological PNS which acts through indirect infiltrations, para-neoplastic cerebellar degeneration causes cerebellar hemisphere enlargement, and Opsoclonous myoclonus (arrhythmias, ataxia, and hyperosmolar-coma like symptoms). It is rare and affects only 0.1% of the cancer patients. Neurological PNS are classified into two categories such as classical and non-classical syndromes. Classical syndromes are diagnosed within 5 years of generation of neurological symptoms, where as in case of non-classical syndromes resolves after cancer treatment with consequent immunotherapy. In non-classical, there are no or very less chances of spontaneous improvement. These syndromes are associated with antineuronal antibodies (Anti-Hu, Yo, CV2, Ri, Ma2, and Amphyphysin), which target the areas such as cranial nerves, retina, CNS, and neuromuscular junction. The onconeural antigens are involved in parts of the brain. CSF evaluation to be done and found that cluster of differentiation 4 (CD4)+T cells and B cells cause loss of neurons in infected areas with inflammatory infiltrations [Figure 1]. Antibodies attaches to cell surface through voltage gated ion channels and membrane receptors such as metabotropic glutamate receptor 1, N-methyl-D-aspartate receptor, and glutamate acid decarboxylase. Classical syndromes are such as cerebral degeneration, limbic encephalitis, Lambert-Eaton myasthenic syndrome, and sensory neuropathy. Non-classical syndromes are such as brainstem encephalitis, stiff person syndromes, necrotizing myelopathy, motor neuron syndrome, acquired neuromyotonia, and acute necrotizing myopathy. In this the tumors involvements are there that expresses the neuroendocrine proteins like neuroblastoma, teratomas like cell targets. During the course of the chemotherapy, it damages the nervous system and causes problems such as encephalitis, neuronal degeneration, and myelopathy.[19] Para-neoplastic cerebellar degeneration is often occurred by flurodeoxyglucose-positron emission tomography found the high level of cerebral metabolism and excess loss of Purkinje fibers that are involved in inflammatory infiltrations in cortical regions. It occurs by vitamin deficiency of thiamine and tocopherol.

FUTURE INTERVENTIONS

In future, there should be development of models for the study of chemotherapy induced CNS toxicity. Pioneer chemotherapeutical study trials is an multiple centered, randomized study trials should be done for the analysis of safety profile, study profile exploration of two drug treatment for toxicity problems, and bio-markers endpoint statistical analysis. Exploring studies should be performing in initiation of during damages in centers of the CNS regulation of gene expression for the regulation of gene expression. Study in the field of alteration in genome methylation of DNA for investigating the real cause of the development of toxicity. There is the need of preclinical model for the development of new endpoint biomarkers for the chemo brain and CNS toxicity studies. New technology should be come into way for the diagnosis of toxicities in CNS. New Geroprotectors should be developed to investigate the damaging effect associated with age.[20] Geroprotectors are used to extend the healthy lifespan. There should be initiation of various cross strain experiments to be done to know about alterations during toxicity studies. Development of safest way to administered intrathecal chemotherapy to reduce various complications in CNS. Advances in the shielded radiation course of action in field of radiotherapy and chemotherapy.

CONCLUSION

Chemotherapy is used to treat cancer but it itself causes toxicity to the CNS. It affects the hippocampus of the brain in which it disturbs the CA, dentate gyrus and entorhinal cortex and causes memory impairment in cancer patients. In cortical regions, it causes lobes, mitochondrial dysfunctions which lead to apoptosis. Chemotherapy (cytarabine, cisplatin, and paclitaxel) induces CNS related syndromes such as PNS, and para-neoplastic cerebral degenerations of brain.

CONSENT OF PUBLICATIONS

Written informed consent was obtained from all the subjects for the publication of this review.

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