



Chemotherapy-Induced Cognitive Impairments: A Systematic and Updated Review

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ABSTRACT

Chemotherapy-induced cognitive impairment or 'chemobrain' is an established clinical syndrome, consisting of cognitive changes in various domains i.e. working memory, executive function and episodic verbal memory that persist only in a subgroup of long-term cancer survivors. However, cancer type, treatment strategy can influence cognitive status. Rodent research has overcome these confounds to systematically evaluate cognitive domains and underlying neural mechanisms disrupted by chemotherapy treatment. In rodents, chemotherapeutic substances have been shown to damage neural precursor cells and white matter tracts and are associated with impairments of learning and memory. Structural and functional changes associated with chemotherapy have also been observed in humans. Besides affecting cancer cells, cytostatic agents also affect healthy cells in the body leading to a number of side effects that generally disappear over time after treatment cessation. Therefore, a systematic review was conducted to examine the relationship between chemotherapy and cognitive decline in animal models, various mechanism involved, and genetic changes occurred etc. Search was performed in PubMed, PsycInfo, Web of Science, Scopus and Medline databases. A quality assessment yielded a total of 52 papers to be considered for the review by using strict inclusion and exclusion criteria.

Keywords: Chemotherapy - induced cognitive impairment (CICI), neuroinflammation, neurogenesis.

INTRODUCTION

Chemotherapy

Chemotherapy agents used for the treatments of cancer patients. Chemotherapy drugs are used to prevent cancer cells from spreading or multiplying to other tissues. Some traditional chemotherapy agents appear to concentrate their effect on cell proliferation. Because cell proliferation is a characteristic of many normal cells, these agents have cytotoxic effects on normal cells¹. Although the blood-brain barrier provides some protection from systemic treatments, it is increasingly recognized that many agents gain access to this environment, via direct or indirect mechanisms, potentially contributing to central nervous system toxicity. Most chemotherapeutic agents, for example antimetabolite (Methotrexate, 5-Fluorouracil), platinum-based agents, or nitrosourea, have been associated with CNS neurological toxicity². Besides, a few factors on creating neurotoxicity related to chemotherapy have been distinguished, including presentation to high-dose regimens³ added substance impacts of simultaneous radiotherapy administration, an intra-arterial organization with BBB interruption or intrathecal administration.^{4, 5} Thus the type of dose and administration route of chemotherapy are all variables of substantial importance in understanding the effect of chemotherapy on cognitive functions.

Chemotherapy induced Cognitive impairment-chemobrain

Chemotherapy - induced cognitive impairment (CICI) is the adverse effect of experienced by most patients during

and after chemotherapy treatment for cancer. CICI is characterized by difficulty with thinking, basic cognitive process, concentrating, and word retrieval additionally as a problem in with efficiency process data secondary to receiving therapy. It has been outlined as "the impairment of patients' learning and memory, concentration, reasoning, executive function, attention, and visuospatial skills during and after discontinuation of chemotherapy."⁶ CICI is additionally referred to as, 'chemotherapy-induced cognitive impairment, and cognitive dysfunction, chemo brain or chemo fog,⁷ the long and short term quality of life (QOL) can be negatively affected by CICI. Studies results vary however have shown CICI to have an effect on 16-75% of cancer survivors.⁶ CICI is an identified condition that's increasing in prevalence with increased survivorship. Physical Therapy improved QOL for cancer survivors with CICI. A significant number, estimated between 18% and 78% of breast cancer patients report dyscognition soon after initiating chemotherapy treatment.^{8, 9} While chemobrain is not an uncommon clinical problem, it is difficult to demonstrate clinically significant cognitive impairment.¹⁰⁻¹² Despite the paucity of evidence for cognitive impairment, patients with chemobrain consistently report clinically important cognitive dysfunction that impair their daily function, in particular in regards to attention, concentration, forgetfulness, word-finding, multi-tasking, and organization.¹³ Another important feature of chemobrain is its common, but not mandatory, relationship to several somatoform symptoms, in particular anxiety, depression and fatigue, and overall health related decline.¹⁴ Studies have described alterations in the blood-brain barrier that allow increased access of cytotoxicity agents to



vulnerable neurons. Neuroimaging studies shows, structural and functional changes in the frontal cortex and white matter tracts that helps in executive and memory function, were affected with Chemobrain.^{15, 16} Evidence to support that oxidative stress, neural repair, immunologic, and endocrine changes in chemobrain are severely limited. These illnesses also draw support from Neuroimaging studies that commonly show alterations in the structure and function of frontal cortical regions that are passing similar to those documented in chemobrain. Limited evidence of alterations in oxidative stress, neural repair, immunologic, and endocrine changes have also been reported. Both of these illnesses have disputed causal triggers, such as trauma in fibromyalgia and infection in chronic fatigue syndrome, whose validity is also not answered by the scientific literature to date. Cancer patients often experience cognitive disturbances associated with chemotherapy during the course of treatment or long after treatment has ceased, a phenomenon is known as chemobrain.⁶ Cognitive impairment occurs in 17–75% of patients, most of whom receive chemotherapy for leukemia and breast cancer.¹⁷ The cognitive domains affected by chemotherapy are diverse. These broad functional impairments stem from changes across multiple regions of the brain as opposed to a single neural substrate. These include the prefrontal, frontal, temporal, and parietal regions. Volumetric changes in grey¹⁸ and white matter,¹⁹ loss of neural connectivity, and reduced glucose metabolism also accompany chemotherapy-induced cognitive impairments (CICI).

Common Symptoms of CICI²⁰

- Trouble concentrating (can't focus, have a short attention span, may "space out")
- Trouble remembering details like names, dates, and sometimes larger events
- Trouble multi-tasking, like answering the phone while cooking, without losing track of one task (they are less able to do more than one thing at a time)
- taking longer to finish things (disorganized, slower thinking and processing)
- Forgetting things that are usually easy to recall (memory lapses)
- Trouble remembering common words (unable to find the right words to finish a sentence)

Risk Factors for CICI²¹

- Radiation therapy to the brain
- Higher doses of chemotherapy or radiation
- Multi-agent chemotherapy combined with radiation
- Brain cancer
- Chemotherapy combined with whole-brain radiation

- Chemotherapy is given directly to the central nervous system
- Hormone changes or hormone treatments
- Immune-related dysfunction
- a genetic predisposition for genes associated with Alzheimer's Disease
- The cancer itself
- Tiredness (fatigue)
- Sleep problems
- Other illnesses, such as diabetes or high blood pressure
- Drugs such as steroids, anti-nausea, or pain medicines. Drugs used during surgery (anesthesia),
- Depression
- Low blood counts
- Age
- Infection
- Nutritional deficiencies
- Stress, anxiety, worry, or other emotional pressure
- Younger age at the time of cancer diagnosis and treatment

Aims and objectives

The aim of this systematic review was to critically evaluate empirical research to determine the occurrence of CICI in animal models. The first objective was an assessment of mechanisms of chemotherapy-induced cognitive impairment and neurobiological processes involved in cognitive impairment. The second objective was an assessment of cognitive domains to determine the strength of evidence in the literature for impairments in short term memory (STM), long term memory (LTM) and executive control. The third objective was an assessment of chemotherapy agents to determine which chemotherapy agents and/or combination of agents have produced the most reliable evidence of impairment. The fourth and final objective was an assessment of the evidence for specific neural mechanisms affected by chemotherapy via tissue analysis and/or the administration of Pharmacological, behavioral or dietary treatments.

Search strategy

Systematic search was performed to examine available literature suggesting a relationship between chemotherapy and cognitive impairment in animal models. A computerized search for peer reviewed journal articles was carried out using PubMed, PsycInfo, Web of Science, Scopus and Medline.



Inclusion and exclusion criteria

The search was limited to research and review articles, excluding papers in languages apart from English, where the subjects were non-human animals. The included reports were screened for quality of papers by using strict inclusion and exclusion criteria.

Identified mechanisms of chemotherapy-induced cognitive impairment in cancer patients

A chemotherapy agent has been proposed to damage the brain by manipulating the permeability of the blood-brain barrier, promoting neuro inflammation and oxidative stress. Some agents including docetaxel,²² cisplatin,²³ carmustine,²⁴ oxaliplatin,²⁵ 5- fluorouracil (5-FU),²⁶ and Paclitaxel²⁷ have been shown to penetrate the BBB in murine models, nonhuman primates and cancer patients. Hence, chemotherapy agents have the potential to directly affect cells of the central nervous system. Indeed, doxorubicin (DOX), DTX, and methotrexate²⁸ have also been shown to damage blood vessel walls in cancer patients, potentially contributing to leakiness of the BBB. In turn, this may disrupt cell survival pathways via the release of inflammatory mediators and free radicals sustaining a further injury to the brain.²⁹ Other mechanisms of chemobrain include impaired neurogenesis, myelin breakdown, and genetic predisposition, decreased hippocampus volume^{30, 31} and hippocampal deformation, an indirect measure of neurogenesis, are evident in leukemia and breast cancer patients up to 18 years post treatment. Chemotherapy also appears to disrupt neural connectivity by attacking the structural integrity of myelin sheaths in white matter. Human post-mortem tissue analyses and stereotactic biopsies reveal myelin loss³² and axonal degeneration in chemotherapy-treated cancer patients. Finally, CICI is also believed to be associated with polymorphisms of genes related to oxidative stress and myelin synthesis including catechol-O-methyl transferase (COMT)³³ nitric oxide synthase and glutathione S-transferase. The mechanisms underlying chemotherapy-related cognitive impairment are not well understood.³⁴ Contrary to the previous belief that systemically administered chemotherapeutic agents have little effect on the CNS, there has been an increasing body of literature in support of toxic effects of chemotherapy on diverse cell populations in the CNS. An overview of chemotherapeutic substances associated with CNS toxicity.³⁴ Have proposed several candidate mechanisms to account for the link between chemotherapy and cognitive impairments. For instance, chemotherapeutic agents cause cellular toxicity via oxidative stress and deoxyribonucleic acid (DNA) damage. Noteworthy, oxidative DNA damage has also been found in cancer patients before chemotherapy and may harm neural function even before treatment initiation. Besides, genetic polymorphisms in DNA repair mechanisms are considered important factors to influence the degree of chemotherapy-associated CNS damage. Other factors linked to cognitive impairment

include activation of neurotoxic cytokines³⁵ and hormonal deregulation³⁴ possibly with additive or synergistic neurotoxic effects. For instance, exposure to the frequently used antimetabolite 5-fluorouracil (5-FU) results in a syndrome of delayed myelin damage³⁶ associated with impaired neuronal impulse conduction and increased latency of auditory brain stem responses in mice. Collectively, reduced white matter integrity and impaired hippocampal neurogenesis are thought to represent major cell-biological mechanisms underlying the typical cognitive complaints seen in cancer survivors including deficits in attention, memory, and processing speed.³⁷ Animal studies offer the possibility to assess cognitive impairments induced by chemotherapy while avoiding numerous potentially confounding factors that impede research in human patients. A further, prospective study in mice treated with a combination of methotrexate and 5-FU showed performance decrements for cognitive tasks acquired pre-treatment including spatial memory, NMTS learning, and delayed NMTS, as well as for new, post-treatment tasks requiring associative and discrimination learning.³⁸ Deficits were thus found again for tasks tapping frontal and hippocampal functions. Besides, the poor performance on the discrimination-learning task known to involve the striatal system suggested more wide spread impairments.

Neurobiological processes involved in cognitive impairment

Several studies have examined whether the behavioral impairments caused by chemotherapy treatment were associated with specific neurobiologies. The studies reviewed below are those that performed tissue analysis, electrophysiology or neuroimaging during or directly after behavioral tasks.

Neurogenesis

Chemotherapy disrupted neurogenesis in the dentate gyrus of the hippocampus. Decreased cell proliferation was evident with 5-FU,³⁹ MTX, TMZ, CMF or CYP+DOX + 5-FU. Decreased survival of immature neural progenitors was evident with cisplatin, CYP, DOX,⁴⁰ 5-FU, MTX, CYP+DOX, CYP+DOX + 5-FU or MTX + 5-FU. The loss of mature neurons was also evident with MTX, CYP+DOX or MTX + 5-FU.

The blood-brain barrier

The blood-brain barrier (BBB), protect brain from potentially harmful compounds. The BBB consist of capillary endothelial cells of the brain, which are closely linked by tight junctions. The Brain endothelial cells lack fenestrations and have low pinocytotic activity and the characteristics build a rigid wall. The physical architecture of the BBB is equipped with a range of efflux transporters that restrict the BBB penetration of drugs.

White matter

5-FU has related to reduce myelin sheets and decrease



olig2 expression that is important for generating functional oligodendrocytes in the corpus callosum of mice.³⁶ White matter and oligodendrocytes are important for neuronal impulse conduction. 5-FU damages white matter that reduces speed of information processing observed in patients after adjuvant chemotherapy.

Mitochondrial dysfunction and oxidative stress

Chemotherapy affects antioxidant defence systems and produced free radicals in the hippocampus,⁴¹ frontal lobe, blood serum and neural tissue homogenates cisplatin, carmustine or doxorubicin were associated with mitochondrial derangement increased lipid per oxidation and the loss of glutathione, glutathione reductase, SOD and catalase.

Neuro inflammation

Chemotherapy up-regulated proinflammatory cytokines and gliosis in the hippocampus,⁴⁰ genu of the corpus callosum (CC), frontal lobe⁴¹ and blood serum. Elevated TNF- α , cyclooxygenase-2 and IL-1 β , microglia and astrocyte reactivity⁴² were associated with Cyclophosphamide, carmustine, and doxorubicin, DTX or CMF.

Targeting cytokine regulation and inflammation

Research shows cytokines are directly involved in cognition in healthy populations and the neurophysiological processes that control complex cognition includes IL-1, IL-6 and TNF. On the other hand, high levels of pro-inflammatory cytokines have been associated with cognitive problems and dementia in the general population. Cytokines have proven useful in the treatment of Alzheimer's disease in clinical studies and in improving cognition in animal models.

Structural abnormalities

Dendrite morphology

Chemotherapy altered dendrite morphology. Cytarabine (Ara-C),⁴³ Cyclophosphamide or cisplatin⁴⁴ reduced dendrite length, volume, spine density, number of branch points and altered dendritic projection paths. Such neuropathologies were evident in apical dendrites of the anterior cingulate cortex (ACC), pyramidal neurons of the cingulate cortex and granule and pyramidal neurons of the hippocampus.

Cellular morphology

Chemotherapy treatment injured the structural integrity of neurons. Carmustine,⁴⁵ cisplatin or vincristine, pyramidal and purkinje cells in the hippocampus and cerebellum, respectively. Cisplatin decreased the volume of nuclei and eosinophilic cytoplasm, swelled synaptosomal mitochondria and soma in both apical and basal pyramidal neurons in the cerebellum and hippocampus.

Fibre orientation

Tangentially orientated fibre bundles, disorientated axons and the loss of myelinated network integrity in the striatum radiatum and medial prefrontal cortex (mPFC) were associated with carmustine treatment.

Apoptosis and autophagy

Chemotherapy initiated programmed cell death, known as apoptosis, in the hippocampus. Carmustine,⁴⁵ cisplatin⁴⁶ or OXP were associated with increased pro-apoptotic protein caspase-3 and caspase-9 enzyme activity, increased apoptotic nuclei and the loss of antiapoptotic protein, B-cell lymphoma 2 (Bcl-2)⁴⁷ Furthermore, DTX elevated cellular stress, known as autophagy, in the hippocampus. Fluorouracil could induce apoptosis in colorectal cancer cell lines through the intrinsic mitochondrial pathway.⁴⁸

Myelin

The loss of myelin basic protein reactivity and oligodendrocyte precursor cells in the genu of the CC, suggestive of myelin degradation, were evident after CMF treatment.

Neurotrophic factors

5-FU was associated with decreased neurotrophic support via the loss of brain-derived neurotrophic factor in the hippocampus.

DNA damage

5-FU was associated with DNA damage marked by higher electrophoretic mobility and longer tail momentum values.⁴⁹ Cisplatin was associated with the loss of postsynaptic density protein 95 (PSD95) expression, important for scaffolding postsynaptic dendrites, and the disruption of mitigated protein activated kinase signaling via the loss of extracellular signal-regulated kinases 1 and 2 (ERK1/2) in the hippocampus, crucial for regulating synaptic plasticity.⁵⁰

Metabolism and cerebral blood flow

Decreased glucose metabolism in the bilateral mPFC and hippocampus was associated with Cyclophosphamide or doxorubicin (DOX) treatment.⁵¹ Decreased 18F-FDG uptake, a marker of regional brain metabolism, was evident in the prefrontal cortex (PFC) after DOX. Bilateral connectivity was also decreased within the sensory-motor network marked by reduced blood flow in the superior colliculus after DOX.

Neurotransmitter systems

Dopamine, nor epinephrine, serotonin and serotonin metabolite levels declined in the hippocampus after methotrexate (MTX) treatment. MTX also increased the glutamatergic acid analog, homocysteic acid, the metabotropic glutamate agonist, homocysteine sulfinic acid and the aspartate analog, cysteine sulfinic acid in the cerebral spinal fluid (CSF). Cisplatin increased acetyl



cholinesterase activity in neural tissue homogenates and decreased acetyl cholinesterase enzyme activity in the hippocampus.⁵² CYP or DOX were associated with decreased expression of choline acetyl transferase activity in the hippocampus. CYP+DOX cocktail chemotherapy was associated with a reduction in $\alpha 7$ nicotinic acetylcholine receptor (nAChR) mRNA expression in the hippocampus.

Electrophysiology

Cisplatin blocked long term potentiating expression at the amygdala- anterior cingulate synapses and altered the physiological expression of theta oscillation. This disrupted synchronicity of the basolateral amygdala-ACC pathway and memory formation. TMZ also reduced endogenous theta activity in the hippocampus by disrupting theta-band response.

Folate

MTX was associated with changes in folate homeostasis by depleting levels of 5- methyl tetrahydrofolate and increasing levels of homocysteine in the CSF and blood serum.⁵³

Auditory gating

MTX + 5-FU were associated with impaired sensory gating of whole brain event related potentials.

Cognitive and neurobiological effects of cytostatic agents in animal studies

Alkylating agents

Alkylating agents alkylate electron-rich atoms to form covalent bonds and the most important antitumor activities are reactions with DNA bases. By functional alkylating agents reacts with each of the atoms of each DNA strand to produce cross link, whereas Mono functional alkylating agent reacts with only one DNA strand. This process prevents cell replicating.⁵⁴ Effect of Cyclophosphamide on cognitive function briefly described in the literature. Literature shows TEPA treatment trigger inhibition in hippocampal cell proliferation and affects the object placement recognition and novel object recognition. These studies include mice or rats that were treated with Cyclophosphamide alone, or in combination with doxorubicin.⁵⁵ Cyclophosphamide does not affect anxiety or cued fear behavior, but it does affects passive avoidance task learning and contextual fear conditioning in rats and memory retention, passive avoidance learning and NOR.⁵⁶ Surprisingly, Lee et al. found that female rats that treated with Cyclophosphamide or 5-Fluorouracil (5-FU) show improved cognition as measured in a Morris water maze (MWM) and a Stone 14-unit T-maze seven weeks after treatment. But this relative improvement was gone after seven months treatment.

Cisplatin and its analogs

The nature of Cisplatin and its analogs is to form a different kind of monofunctional and bifunctional adducts that lead to the formation of intrastrand or interstrand DNA cross-links. These adduct formation interrupts number of cellular processes such as separation, replication, and transcription.⁵⁴ while the platinum drugs yet not been briefly studied for their effects on cognition in animal models. Some unpublished work has shown that administration of platinum drug to healthy animals (oxaliplatin) impairs novel object recognition, spatial reference memory and contextual fear condition. Furthermore, it is more affective when oxaliplatin is giving with 5-FU. Many studies show these drugs affect several neurobiological processes, including oxidative stress, apoptosis.

Anti metabolites

The metabolic substance which affects the biosynthesis or the function of nucleic acids and impairs the formation of new DNA or RNA is known as antimetabolites. The most frequently studied antimetabolites concerning cognitive behavior are methotrexate (MTX) alone⁵⁶ and 5-FU alone as well as their combination. However, one paper has shown cytosine arabinoside appears to affect remote recall of MWM spatial location but not acquisition or recent recall in the MWM in rat.⁴³ MTX is an inhibitor of dihydrofolate reductase, an important enzyme in folate metabolism. This enzyme maintains the intracellular folate pool which serves as a carrier for the synthesis of thymidylate, purine nucleotides, and certain aminoacids. Methotrexate show a variety of cognitive impairments, spatial MWM learning, NOR,⁵⁸ object placement recognition, conditioned emotional response, and operant response learning.⁵⁶ Similarly, 5-FU treatment alone impairs object placement recognition and retrieval of a learned operant response.⁵⁶ methotrexate has been found to have some neurobiological effects, reduced neurogenesis, reduced blood flow/glucose metabolism, increased neurotoxic effects, apoptosis, oxidative stress, and white matter damage.

Anti microtubule agents

Microtubule forms the mitotic spindle that is responsible for the separation of replicated DNA disruption of the dynamics of microtubule by antimicrotubule agents interferes with cell division and proliferation. Antimicrotubule agents may disrupt many of the non mitotic functions of microtubules, such as Chemotaxis, membrane, intracellular scaffolding, transport, secretion, and/or anchorage of organelles and receptors, adhesion, locomotion, and mitogenic signaling.⁵⁴ Paclitaxel is an antimicrotubule agent associated with cognitive impairment in patients. However, similar to doxorubicin, paclitaxel that does not cross the blood-brain barrier readily. Paclitaxel is also a very good substrate for P-glycoprotein; knockout mice deficient in P-glycoprotein



show brain exposure to paclitaxel 10-fold higher than wild-type controls.

Cognitive domains

The pre-clinical literature was reviewed to determine the evidence of functional impairments across broad cognitive domains. The papers using animal models predominantly used behavioral tests that rely on various forms of short term memory (STM), long term memory (LTM) and executive control.

Short term memory

Spatial working memory

Morris water maze. Short term memory is assessed within the standard Morris Water Maze (MWM) task when the probe trial is conducted within a training session or shortly after the last training trial. Spatial recall in the probe trial is often determined via changes in time searching the target quadrant containing the escape platform. Cisplatin,⁵⁹ vincristine and MTX + 5-FU reduced time spent in the target quadrant, whilst other studies reported MTX + 5-FU, CYP + DOX + 5-FU⁶⁰ or CYP+DOX had no effect. Furthermore, some studies have sought to examine the dose dependent effect of chemotherapy drugs and potential longitudinal changes. Rats administered a high dose (0.55 mg/ml) vincristine spent less time spent in the target quadrant compared to rats administered a lower dose (0.06 and 0.18 mg/ml). In addition, longitudinal studies have also shown that MTX + 5-FU reduced time spent in the target quadrant at 1 week and approximately 3 months post treatment cessation.³⁸ Spatial recall in the probe trial is also determined via swim path length and target quadrant entries or crossings. Cisplatin, vincristine and CYP+DOX reduced swim path length in the target quadrant. CYP+DOX also reduced the number of entries into the target quadrant. CYP+DOX+5-FU reduced the number of target platform crossings, whilst this impairment was not observed with cisplatin or vincristine.

Y-maze spontaneous alternation test.

Three studies have examined the effect of chemotherapy on spatial working memory in the Y-Maze spontaneous alternation task. Cisplatin and CYP+DOX⁶¹ reduced spontaneous alternation.

Barnes maze. The effect of chemotherapy on spatial working memory has also been examined using the Barnes Maze. Mice treated with 5-FU, topotecan or a higher dose of DOX (10 mg/kg) spent less time in the escape zone during the probe trial when the difference between treatment initiation and testing was 1 month. These cognitive deficits were not observed with CYP, DTX, MTX or a lower dose of DOX (5 mg/kg). No impairments were observed during training or when the difference between treatment initiation and testing was 121 days for all treatment regimens.

Radial arm maze. In another test of spatial working memory, rats treated with carmustine made more errors and required more trials to reach criterion.⁶² In a water-maze version of this test, rats treated with carmustine made an increased number of errors by entering “non-escape arms” as opposed to the “goal arm” during training and test.⁴⁵

Delayed spatial alternation task (DSAT)

The DSAT was used to determine how chemotherapy influences the ability to remember which of the 2 levers had been last pressed in a Skinner box. CYP lowered the portion of correct responses and increased the ratio of responses per reward as a function of time, with greater delay intervals producing the most profound memory deficits.⁶³

Delayed N-matching to sample

A spatial version of the DNMTS task has been used to examine the effects of chemotherapy on spatial cue memory with a temporal delay, designed to increase task difficulty. Mice treated with MTX + 5-FU increased the amount of errors as a function of delay interval.³⁸

Recognition memory

The novel location recognition. The novel location recognition (NLR) task takes advantage of an animal's natural curiosity to investigate objects in their environment that are placed in novel locations and to ignore objects that are placed in familiar locations. The short term version of this task employs retention intervals of less than 4 h. Monotherapy with MTX,⁶⁴ 5-FU,³⁹ CYP, DOX, DTX or oxaliplatin (OXP) reduced preference scores for the newly located object. However, other studies reported that CYP did not impair location recognition memory. Two studies examined recognition memory by combining the novel object recognition (NOR) and NLR tasks into a single behavioral paradigm. Cisplatin reduced preference scores for the novel object positioned in a new location.

Novel object location recognition. The NOR task uses the natural tendency of an animal to preferentially investigate novel object compared to familiar objects.⁶⁵ The short term version of this task employs retention intervals of less than or equal to 2 h. Monotherapy with carmustine, MTX, DOX, DTX OXP or 5-FU reduced preference scores for the novel object. However, other studies have shown that monotherapy with DOX, 5-FU, DTX, MTX or OXP did not alter preference scores for the novel object. Cocktail chemotherapy with CMF lowered preference scores for the novel object. However, CYP+DOX did not impair object recognition memory.

Long term memory

Spatial working memory

Morris water maze. Escape latencies, distance travelled and number of the target quadrant entries to find the hidden platform during training is used to measure



spatial learning or acquisition. Monotherapy with cisplatin⁶⁶ or vincristine⁵⁹ increased escape latencies during training. However, treatment with Ara-C, DTX, MTX, 5-FU or OXP had no effect on escape latencies. Cocktail chemotherapy with CYP+DOX + 5-FU,⁶⁰ MTX + 5-FU or CMF increased escapes latencies during training. However, treatment with OXP + 5-FU or CYP + 5-FU did not impair escape latencies. Furthermore, studies that examined the dose dependent effect of Vincristine reported that a higher dose (0.55 mg/ml) impaired escape latency and distance travelled to the platform, with lower doses (0.06 and 0.18 mg/kg) failing to produce impairment.

Contextual memory

Contextual fear. Chemotherapy has been shown to induce deficits in contextual fear with both single and multiple tone-shock pairings. Monotherapy with DOX,⁴⁰ 5-FU,³⁹ cisplatin⁴⁶ or CYP reduced freezing levels to the conditioned context 24 h after conditioning. In addition, OXP impaired renewal of a conditioned response 24–48 hours after extinction. However, several studies have reported that DOX,⁶⁷ cisplatin,⁶⁸ 5-FU or OXP did not impair contextual freezing 24 h after conditioning suggesting no impairment of conditioned acquisition.

Recognition memory

Novel location recognition. The long term version of this task employs retention intervals of typically 24 h and is slightly impaired in chemotherapy-treated animals. Monotherapy with CYP or DOX did not reduce preference scores for the newly located object.⁴⁰ Whilst impairments with thiotepa were only evident at 20 weeks post treatment cessation.⁶⁹

Novel object recognition. Similar to NLR, the long term version of this task employs retention intervals of 24 h. Monotherapy with methotrexate⁵⁶ or cisplatin reduced preference scores for the novel object. However, whilst cocktail chemotherapy with MTX + 5-FU did not impair preference scores for the novel object, these mice showed increased exploration time suggesting hyper arousal. Stimulus-response learning Cued Memory. The cued memory paradigm is a variant of the water maze task in which the platform location is indicated by a visual cue. MTX + 5-FU did not impair stimulus- response learning as chemotherapy-treated mice spent ample time in the platform-cue zone at test.³⁸

Conditional associative learning. The effect of chemotherapy on recognizing spatial cues that signal the direction of an escape platform in a cross-maze has been examined in one study. Mice treated with MTX + 5-FU made more errors, having difficulty associating an environmental cue with the platforms spatial context. However, cognitive impairments were only evident a few weeks after treatment cessation, not evident during a 3 month follow up.³⁸

Cued fear. Chemotherapy does not appear to disrupt

cued fear in both single and multiple tone-shock paradigms. Monotherapy with DOX,⁴⁰ 5-FU,³⁹ cisplatin,⁴⁶ CYP⁴⁰ or OXP,⁷⁰ did not reduce freezing levels to the conditioned stimulus (CS) 24–48 hours after conditioning. Cocktail chemotherapy with CYP + 5-FU prior to acquisition did not disrupt cued fear 4 months after conditioning.

Avoidance learning

Conditioned avoidance. Methotrexate has a dose dependent effect on avoidance learning when a warning signal predicts a foot shock. Low (1.5 mg/kg) and high dose (2 mg/kg) MTX reduced the number of compartment crossings to avoid a foot shock. The rats with higher dose of MTX performed significantly worse.⁷¹ Cisplatin does not produce cognitive impairment shortly after treatment but, when re-tested 2–4 weeks later, cisplatin-treated mice shows increased escape latencies and a reduced number of compartment crossings.

Passive avoidance. Many experiments tested the impact of chemotherapy on learning, to avoid a context paired with foot shock. Monotherapy with MTX,⁷² OXP,⁴⁷CYP, DOX or cisplatin and combination chemotherapy with CYP+DOX reduced cross over latencies into the back compartment previously paired with shock as well as reduced freezing levels. However, carmustine did not impair cross over latencies.⁶²

Executive control

Discrimination learning (rule learning and behavioral inhibition)

Stone 14 unit T-maze.

Cocktail chemotherapy with 5-FU+CYP resulted in rapid learning in the Stone 14 Unit-Maze task. Chemotherapy-treated rats exhibited a steady decline in the number of errors by successfully navigating themselves through the maze with correct discriminations in order to avoid a foot shock. Monotherapy with 5-FU or CYP also resulted in rapid learning. However, superior performance was only evident at 9 weeks post treatment in infant rats as opposed to 42 weeks. More so, aged rats tested at 16 weeks post chemotherapy treatment performed no differently to controls.⁷³

Genetic changes associated with chemobrain

Nowadays, it is generally accepted that long-term cellular memory is mediated by epigenetic phenomena and global DNA methylation, which is associated with changes in the cytokine milieu.⁷⁴ Epigenetic encompasses an array of heritable modifications of DNA that regulate gene expression and function without altering the acquired DNA nucleotide sequence. Some modified DNA methylation and hydroxyl methylation, histone modification, and non- coding RNA regulation.⁷⁵ Emerging studies indicate that epigenetic regulation of gene expression is involved in various brain-related disorders, such as addiction, depression, stress and Alzheimer's



disease, that genetics alone cannot entirely explain.⁷⁶⁻⁷⁹ Recent studies have indicated that epigenetics, in particular DNA methylation and histone acetylation, plays critical roles in brain development, memory formation, and more importantly, in regulation of learning and memory.⁸⁰⁻⁸³ As detailed above, the various chemotherapy regimens used to treat cancer have a wide range of biologic effects. Also, the metabolic alterations induced by chemotherapy, such as alterations in cytokines, tend to be short-lived⁸⁴ but the experience of dyscognition is often chronic. There is some early evidence to support the role of epigenetic change in chemobrain. Learning and memory impairments following CMF (CYP, MTX, 5-FU) chemotherapy were found to be associated with increased histone H3 acetylation and decreased DHAC (Histone deacetylase) activity in the hippocampus in an animal model.⁸⁵ This chromatin remodeling leads to a decrease in neural cell proliferation in the hippocampus that might be the plausible mechanism in explaining persistent dyscognition after chemotherapy exposure as the DNA methylation induced by cytokines is transient and reversed in two weeks after cytokines are removed from the environment. An association between the development and persistence of chemotherapy-induced neuropsychological disorders and epigenetic changes following chemotherapy treatment was recently shown in breast cancer patients. While the evidence is far from conclusive, the authors hypothesize that the administration of chemotherapy agents initiates a cascade of biological changes, with short-lived alterations in the cytokine milieu inducing persistent epigenetic alterations. These epigenetic changes eventually lead to gene expression changes, altering metabolic activity and neuronal transmission that are responsible for generating the subjective experience of cognition. This proposed mechanism may also explain the inconsistencies observed from neuroimaging findings in patients with mild to moderate self-reported cognitive dysfunction is a subtle process triggered by cytokine deregulation and epigenetic changes that arise from the damage in the brain caused by chemotherapy.

Treatments

Several studies have examined whether chemobrain can be reduced by Pharmacological, behavioral, environmental or dietary treatments. The majority of studies reviewed below examined the strength of these treatments within a single behavioral task at one time point post treatment. However, only 2 studies examined the efficacy of Pharmacological agents in eliminating cognitive impairment within a single behavioral task at multiple time points post treatment.

Pharmacological treatments

Antidepressants.

The serotonin re-uptake inhibitor, fluoxetine has been investigated as a potential treatment for CICI. Fluoxetine placed in drinking water counteracted 5-FU or MTX

location recognition memory impairments. Fluoxetine had a preventative effect in 5-FU treated animals and a reversal effect in MTX treated animals. Fluoxetine counteracted the reduction in cell survival and cell proliferation in the DG of the hippocampus.^{39, 64}

Antioxidants

The use of antioxidants as potential treatments suggest that oxidative stress may mediate cognitive dysfunction during chemotherapy. Injections with N-acetylcysteine prevented CYP+DOX⁸⁶ or cisplatin⁴⁶ impairments in passive avoidance and contextual fear.⁴⁶ N-acetylcysteine also partially mitigated cisplatin-induced object recognition and context-object discrimination memory impairments.

Anti-inflammatory

Anti-inflammatory processes are believed to initiate a deleterious cellular cascade during chemotherapy. The selective COX-2 inhibitor NS-398, rescued object recognition and temporal order memory impairments in Cyclophosphamide, methotrexate, 5-FU (CMF) treated animals. NS-398 blocked inflammatory processes by decreasing the levels of proinflammatory cytokines, TNF- α , IL-1 β and COX-2 in the genu of the CC. NS-398 also significantly attenuated white matter pathologies by restoring myelin sheath thickness in genu of the CC.⁸⁷

NMDA inhibitors

N-methyl-D-aspartate (NMDA), involved in glutamate excitatory transmission, is a key player in memory formation and cognitive mapping in the hippocampus. The NMDA antagonist, dextromethorphan reversed impairments in the NOR task at 1 and 2 months post MTX treatment. The NMDA receptor inhibitor, memantine reversed impairments in the MWM in cisplatin-treated animals. Memantine treatment restored the loss of PSD95 and ERK1/2 protein expression, both crucial for regulating synaptic plasticity, important for learning and memory in cisplatin-treated animals.

Phosphodiesterase and acetyl cholinesterase inhibitors

The phosphodiesterase inhibitor, rolipram known to be important in regulating microtubule dynamics via stabilization of cyclic adenosine monophosphate signalling, reversed location recognition memory impairments in DTX-treated animals.⁸⁸ The acetyl cholinesterase inhibitor, donepezil, known to expedite synaptic acetylcholine to boost cholinergic neural pathways, restored impairments in the passive avoidance, MWM, NMTS and DNMTS tasks in CYP, DOX or MTX + 5-FU-treated animals. Donepezil increased glucose metabolism in the mPFC, parietal cortex and hippocampus in CYP or DOX-treated animals.

Nicotine

Nicotine and its derivative, cotinine, enhance learning and memory via the nAChR system. Treatment with nicotine and cotinine restored location recognition



memory and spontaneous alternation impairments in CMF or CYP+DOX treated animals.⁸⁹ Chronic nicotine treatment reinstated $\alpha 7$ nAChR mRNA expression and cell proliferation in the hippocampus in CYP+DOX-treated animals.

Other pharmacological interventions

Copper sulphate, that impedes OXP cellular transport, prevented impairments in social recognition memory and passive avoidance. Copper sulphate decreased caspase-3 and 9 apoptic protein levels, increased Bcl-2 anti apoptic protein levels and limited the production of free radicals by increasing cytosolic cytochrome activity in the hippocampus.⁴⁵ Production of the neuroprotectant metallothionein by administration of zinc sulphate, prevented spatial working memory impairments in the radial arm water maze in carmustine-treated animals. Pre-treatment with zinc sulphate increased reduced glutathione reductase activity, decreased caspase-3 apoptotic protein levels and retained intact morphology of neurons in the hippocampus. Zinc sulphate also decreased levels of the proinflammatory cytokine, TNF- α in the blood serum.⁴⁷ Pre-treatment with the anti-diabetic, metformin, prevented object, location and social recognition memory impairments in cisplatin-treated animals. Metformin maintained myelinated fibre network integrity, dendritic spine density and branching in the cingulate cortex.⁴⁴ Finally, co-administration of glucose with 5-FU prevented hyper reactive responses to novelty in the NOR task whilst increasing the survival of immature neural progenitors in the hippocampus.⁹⁰

Behavioral Interference

Exercise

There are evidences that show physical activity improves cognitive function.⁹¹ While physical activity has a mild effect on cognition in healthy people, it's also has particularly beneficial effect on people suffering from cognitive impairment illness (e.g. Alzheimer's disease, depression) or aging.⁹² Importantly, physical activity improves the domain of cognition affected by chemotherapy; namely working memory and executive processing. Besides, exercise improves cognitive function by affecting the nervous system that is impaired by chemotherapy: cell proliferation and survival in the hippocampus; Oxidative stress; Integrity of white matter; Inflammation; CNS blood flow through the production of vascular endothelial growth factor; And a series of neurotransmitter systems.

Toremind

In animal models of cognition, hippocampus lesions before training leads to the impaired acquisition of spatial memory, whereas post-training hippocampus lesions leads to impaired performance in test trials of spatial memory.⁹³ However, if these lesions are partial, the mice are reminded of the spatial location, simply contacting for the task can recall the original pre-lesion

location of the stage.⁹⁴ These simple 'reminding' strategies can be effective in reducing cognitive impairment due to the methotrexate. Specifically in the rat that shows impaired spatial memory missed four months post-treatment due to MTX were as control was able to perform at a level later given 2 re-training trials.

Dietary treatments

Anti-inflammatory and antioxidants

Walnuts⁵⁹ and ergothioneine prevented impairments in spatial recall in the MWM and avoidance learning in cisplatin-treated animals. Walnuts protected against neural changes in the CA1 of the hippocampus including shrunken nuclei and eosinophilic cytoplasm. Ergothioneine supplementation prevented the rise of acetylcholine enzyme activity and lipid peroxidation. Compound K, the intestinal metabolite of ginseng, ameliorated inhibitory learning impairments in CYP-treated animals. The flavonoid, rutin, prevented the development of object recognition memory impairments in DOX-treated animals. Rutin reduced levels of TNF- α and increased antioxidant defence systems including catalase, glutathione and SOD in the hippocampus and frontal lobe. Curcumin, a biologically active component of turmeric, alleviated MWM spatial recall impairments in cisplatin-treated animals. Curcumin decreased lipid peroxidation whilst increasing SOD in the hippocampus and blood plasma. Fish oil given to 5-FU or CYP+DOX-treated animals due to its high omega 3 content, did not reverse spatial recall impairments in the MWM or enhance the survival, differentiation and proliferation of cells in the DG of the hippocampus.

Surgical treatments

Stem cell transplant

Transplantation of human cranial stem cells (HCSC) bilaterally into the hippocampus reversed impairments in location recognition memory, temporal order and contextual fear in Cyclophosphamide -treated animals. HCSC intervention minimized reactive microglia and increased granule and pyramidal neuronal length, volume and interactions in the CA1 and DG of the hippocampus.

Neuroimaging studies

Structural and functional neuroimaging have been applied to examine the neural substrate of these cognitive changes in cancer patients. Voxel-based morphometry (VBM) and diffusion- tensor imaging (DTI) are structural neuroimaging techniques capable for detect alterations in gray matter (GM) and white matter (WM) tissue, commonly. Further, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies are functional neuroimaging techniques that can contribute to detect differences in brain functioning even when there is no clear structural damage. Hence, neuroimaging studies provide a fine-grained examination of neural changes correlate with



chemotherapy that are relevant for a better understanding of the natural history of chemotherapy neurotoxic effects. A large number of investigations are performed using such techniques in cancer populations. The purpose of this review was to summarize the current literature on the effects of chemotherapy-related cognitive changes with a focus on structural and functional neuroimaging studies.

Concluding remarks

For some cancer survivors cognitive impairment is a long-term side effect of adjuvant chemotherapy which can have a large impact on quality of life. While many clinical studies have been performed to describe the nature and severity of cognitive impairment, these studies have been unable to adequately explore and identify possible causal mechanisms involved due to, for example, methodological and ethical constraints. Furthermore, these studies have been unable to clearly show which cytostatics are causally involved in cognitive impairment and which individuals are most at risk of developing cognitive impairment. Due to the impact of cognitive impairment on the quality of life and the individual variation in the occurrence and severity of this phenomenon, there has been an increase in the number of animal studies performed during the last years. However, comparisons between these studies are difficult due to differences in species, gender, age of the animals, cytostatic used, treatment strategy, and route of administration, time between treatment and testing, and behavioral tasks used in the various studies. Despite this, several possible pathways that may contribute to the cognitive impairment observed after chemotherapy have been elucidated including inhibition of neurogenesis. While the studies are based on a variety of cytostatic agents, this review indicates that each of these pathways may contribute to the behavioral consequences of chemotherapy. However, it is hard to conclude which brain pathways are directly affected by cytostatic agent, and which pathways are secondarily affected via changes in e.g. vascularization or peripheral factors. There is still a clear lack of systematic studies exploring effects of single cytostatic compounds within different classes on a range of neurobiological mechanisms paired with an appropriate cognitive-behavioral measure. While far from complete, the research conducted thus far suggests that several cytostatics are implicated in cognitive changes post-treatment in rodents. These investigations are important as using animal models has enabled researchers to explore likely causal mechanisms and provide targeted candidates for therapeutic and remedial intervention.

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