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Review article

Chemotherapy-induced cognitive impairment (CICI): An overview of etiology and pathogenesis

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ABSTRACT

Many cancer patients treated with chemotherapy develop chemotherapy-induced cognitive impairment (CICI), often referred to as chemo-brain, which manifest during or post-treatment with variable degrees, onset and duration thereby affecting the patients' quality of life. Several chemotherapeutic agents have been studied to determine its possible association with cognitive impairment and to fully comprehend their contribution to CICI. A vast number of studies have emerged proposing several candidate underlying mechanisms and etiologies contributing to CICI such as direct neurotoxicity, BBB disruption, decreased hippocampal neurogenesis, white matter abnormalities, secondary neuro-inflammatory response and increased oxidative stress; however, the exact underlying mechanisms are still not well defined. This review summarizes CICI associated with most commonly used chemotherapeutic agents with emphasizes the possible underlying pathogenesis in both animal and clinical studies.

1. Introduction

Chemotherapy is the most commonly implemented strategy in cancer treatment, often used in conjunction with radiotherapy, surgery and/or hormonal treatment. Although chemotherapy is beneficial against several malignancies, it also affects healthy cells causing several adverse effects among which central nervous system (CNS) toxicity, including cognitive impairment, is of particular concern [1]. This cognitive impairment "often referred to as chemo-brain, chemo-fog, or chemotherapy-induced cognitive impairment (CICI)" is characterized by the impairment of patients' memory, learning, attention, concentration, reasoning, processing speed, executive functions, and visuo-spatial skills in various types of solid tumors, mainly breast, lung, prostate, and ovarian cancers among others [2–3]. This cognitive impairment varies widely among patients, being transient with mild reversible manifestations (occurring during and after discontinuation of chemotherapy) in most cases. However it can last for years with more severe progressive manifestations in others thereby having a deleterious impact on patients' quality of life [3]. For a given chemotherapeutic drug, the occurrence of CICI and CNS toxicity will depend on several factors, including the total dose, route of administration, presence of structural brain lesions, exposure to prior or concurrent irradiation, and interactions with other drugs [4].The extent to which chemotherapy treatment itself is responsible for any cognitive dysfunction in cancer survivors remains somewhat controversial. Interestingly, a number of studies revealed that cancer patients exhibit neurocognitive deficits manifested prior to chemotherapy [5–6], leading to hypothesized association of these cognitive deficits with cancer itself [7], its related psychological stress and other factors that need to be taken into consideration [8]. Even though these studies are scarce, they suggest that chemo-brain has to be extended to include cancer-induced cognitive impairments (CICI). That being said, full understanding of the cognitive impairment in cancer survivors is still lacking with many researches proposing CICI to be the major contributor. This review will emphasize CICI reported with some of the most commonly used chemotherapeutic agents with its possible underlying mechanisms.

2. Cognitive and neuropsychological effects of chemotherapeutic agents

While many chemotherapeutic agents have been used for cancer treatment, only a small number have been studied for their effects on

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Table 1
Summary of different chemotherapeutic agents' cognitive effects in Experimental studies (animal models).

Class	Drug	Cognitive performances or impairment detection	Doses administered	Comments	References
Alkylating agent	Cyclophosphamide	- Impaired memory retention - Impaired passive avoidance learning - Impaired NOR - Impaired 12 h after therapy - Unimpaired 10 days after treatment	- Mice treated with (40 or 200 mg/kg, i.p.) - Mice treated with (40 mg/kg, i.p.)	- No effect on anxiety behavior	[14] [17]
	ThioTEPA	- Impaired recognition and spatial memory - Impaired NOR - Impaired 8 and 12 weeks after treatment - Unimpaired 2, 4, 20, or 30 weeks after treatment	- Mice treated with (10 mg/kg, i.p.)	- No depression-related behavior	[25]
	Oxaliplatin	- Impaired NOR	- Rats treated with (8 or 12 mg/kg, i.p.)	- Unimpaired spatial memory - Unimpaired contextual fear condition	[11]
Antimetabolite agent	MTX	- Impaired spatial memory - Impaired NOR - Impaired passive avoidance learning	- Rats treated with (37.5-300 mg/kg and 250 mg/kg, i.v.)		[26]
		- Impaired spatial memory	- Rats treated acutely (250 mg/kg, i.p.) or chronically (1 mg/kg, i.p.)	- No significant alteration in visual memory - No significant motor function impairment	[27]
		- Impaired memory and learning	- Rats treated with (1 or 2 mg/kg, intracerebroventricular injection)	- No anxiolytic activity	[28]
	5-FU	- Impaired spatial memory - Impaired object placement recognition	- Rats treated with (20 mg/kg, i.v.)		[31]
		- Impaired memory and learning	- Mice treated with (3, 30, 75 mg/kg, i.p.)		[32]
Combined antimetabolites	MTX + 5-FU	- Impaired spatial memory - Impaired learning and working memory	- Mice treated with MTX (37.5 mg/kg, i.p.) + 5-FU (50 mg/kg, i.p.)		[33]
Cytotoxic antibiotic	DOX	- Impaired inhibitory avoidance conditioning	- Rats treated with (7 mg/kg, i.p.)	- Unimpaired passive avoidance - Induce depressive-like behaviors	[40]
Hormonal therapy (SERM)	Tamoxifen	- Impaired retrieval functions	- Mice treated with (1, 3, 10 mg/kg, i.p.)	- Unimpaired new memory acquisition	[53]
Antimicrotubule agents	Paclitaxel	- Impaired learning - Impaired spatial memory (inconsistent)	- Mice treated with (20 mg/kg, i.p.)		[69]
		- Impaired learning of new rules	- Rats treated with (2 mg/kg, i.p.)	- No spatial and episodic memory impairment	[70]
	Docetaxel	- Impaired long-term spatial memory (Hippocampal-dependent) - Mood impairment	- Rats treated with (1 mg/kg, i.v.)	- Induce depressive-like behavior - No anxiety-like behavior	[62]
		- Impaired NOR - Short-term impaired cognitive memory	- Rats treated with (6, 10 mg/kg, i.p.)		[63]
		- Impaired spatial memory -Impaired object recognition memory	- Mice treated with (32 mg/kg. i.p. either intermittently or via a sustained delivery system)		[64]
		- Impaired hippocampal recognition memory	- Mice treated with (33 mg/kg. i.p.)	- Affected spontaneous behavior	[73]
Combined therapy (alkylating agent + antimetabolite)	Oxaliplatin + 5-FU	- Impaired spatial memory - Impaired NOR - Impaired contextual fear condition - Impaired spatial memory long after treatment	- Rats co-treated with Oxaliplatin (8 or 12 mg/kg, i.p.) + 5-FU (75 mg/kg, i.p.)	- No effect on cued fear recall “A non-hippocampal task”	[11]
Combined therapy (cytotoxic antibiotic + alkylating agent)	DOX + Cyclophosphamide	- Impaired passive avoidance learning(short-term memory impairment, 24 h)	- Rats co-treated with DOX (2.5 mg/kg, i.p.) + cyclophosphamide (25 mg/kg, i.p.)	- No effect on anxiety behavior	[15]
		- Impaired learning and memory - Impaired contextual fear condition	- Rats co-treated with DOX (4 mg/kg, i.v.) + cyclophosphamide (40 mg/kg, i.v.)	- Unimpaired cue-specific fear memory	[16]

(*continued on next page*)

Table 1 (*continued*)

Class	Drug	Cognitive performances or impairment detection	Doses administered	Comments	References
ICIs alone or combined with radiation	Immunotherapy + radiation	- Decreased measures of anxiety - Impaired object recognition - Enhanced neuro-inflammation but not neuro-degeneration		- No phenotype difference - No difference in exploratory activity - No difference in sensorimotor function - No difference in contextual memory	[86]

Abbreviations- NOR: novel object recognition; MTX: methotrexate; 5-FU: 5-Florouracil; DOX: doxorubicin; SERM: selective estrogen receptor modulators; ICIs: Immune checkpoint inhibitors.

cognition and brain. Commonly used chemotherapeutic agents have shown to adversely affect cognitive functions particularly those dependent on the hippocampus and frontal lobes in some animal models [9–12]. Here we will discuss effects of some of the most studied chemotherapeutic agents on cognitive functions in experimental studies and clinical trials as summarized respectively in Tables 1 and 2.

2.1. Alkylating agents

They are DNA-binding alkylating agents leading to apoptotic cell death when the DNA damage exceeds the cell ability to repair. Alkylating agents can be mono-functional reacting with one strand of DNA or bi-functional reacting with two strands of DNA producing cross-links preventing cell replication [13]. Cyclophosphamide effect on cognitive functions has most frequently been described in both clinical and animal studies, either when used alone or in combination with other chemotherapeutic agents. It was shown that cyclophosphamide did not affect anxiety behavior [14–15] or cued fear when studied in animal models [16]. However, cyclophosphamide impaired memory retention [14], passive avoidance learning and novel object recognition (NOR) 12 h after chemotherapy, while being unimpaired 10 days after treatment [17].

In a clinical study performed on women treated with cyclophosphamide, methotrexate, and fluorouracil (CMF) with or without tamoxifen, cognitive impairment was clearly observed 2 years after treatment when compared with the control group associated with memory problems (21% vs. 3%) and concentration problems (31% vs. 6%) [18]. Additionally, in early stage breast cancer patients who received between 3 and 18 months of CMF chemotherapy, similar results were observed when compared with healthy individuals. These observed cognitive impairment effects were found to be positively correlated with the treatment duration of chemotherapy, yet unrelated to other treatment variables as type of chemotherapy [19]. A clinical study showed that CICI may persist more than 20 years after treatment (particularly with CMF treatment) [20], and could be attributable to a decline in hippocampal neurogenesis [21]. Similarly, breast cancer patients treated with 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) showed the most prominent cognitive impairment, particularly in learning and memory, attention, and processing speed. Notably, about one half of the patients who developed cognitive impairment, showed improvement in their cognitive performances one year after the treatment [22]. Additionally, breast cancer patients receiving high dose of combined chemotherapeutic agents (fluorouracil, epidoxorubicin and cyclophosphamide followed by high-dose of cyclophosphamide, thiotepa and carboplatin), showed significantly more cognitive impairment than those receiving either standard dose adjuvant chemotherapy (fluorouracil, epidoxorubicin, and cyclophosphamide) or no chemotherapy. These cognitive effects were observed approximately 2 years after the chemotherapy course, hence suggesting the long term cognitive deficits associated with these chemotherapeutic agents [23].

Moreover, ThioTEPA, another alkylating agentthat has been shown to induce cognitive impairment in some studies through the inhibition of hippocampal cell proliferation [24–25]. In mice, it was found that thioTEPA impaired the novel object recognition 8 and 12 weeks after treatment, although they were not impaired 2, 4, 20, or 30 weeks after treatment [25].

Lastly, the chemotherapeutic platinum drugs, although they have not yet been extensively studied for their effects on cognition in animal models, some investigations reported an associated cognitive dysfunction. When administered in healthy rats, oxaliplatinhas shown to impair novel object recognition. Furthermore, in another study where oxaliplatin is administered in combination with 5-FU, spatial reference memory, and contextual fear condition impairment was noticed, thus indicating the deteriorating role of oxaliplatin in cognition [11].

Table 2
Summary of different chemotherapeutic agent's cognitive effects in clinical trials.

Drug & class	Cognitive performances or impairment detection	Clinical participants	Randomization and control methods	Chemotherapeutic treatment	References
Tamoxifen "hormonal therapy (SERM)"	- Impaired memory - Impaired processing speed - Impaired visuospatial functioning	- Pre-menopausal women with early breast cancer (n = 23)	-A cross-sectional design study Control group consists of age matched, healthy women not using tamoxifen (n = 23)	- Tamoxifen treated patients for at least 30 days (20 mg/ml), with no prior exposure to chemotherapy	[51]
	- Impaired verbal fluency	- Breast cancer patients who had previously participated in a population-based case-control study of 2653 women with breast cancer	- A follow-up study of breast cancer women of a previous study with their matched controls of non tamoxifen users	- Tamoxifen users were classified by their duration of use as standard-term users (4–5 years), short-term users (< 4 years) or long-term users (6+ years)	[52]
CMF (± tamoxifen) "combined therapy; alkylating agent +antimetabolite agents (± SERM)"	- Impaired verbal and visual memory - Impaired concentration and attention - Impaired mental flexibility - Impaired processing speed - Impaired motor function	- Primary breast carcinoma patients with metastasis to axillary lymph nodes treated with adjuvant chemotherapy (n = 39)	- Patients were not randomly assigned to adjuvant chemotherapy - The control group composed of age-matched patients with axillary lymph node negative breast carcinoma who received the same surgical and radiation therapy but not the adjuvant chemotherapy (n = 34)	- Treated with adjuvant CMF (6 courses; cyclophosphamide 100 mg/m2, p.o. on days 1–14, MTX 40 mg/m2 i.v. on days 1 and 8, and 5-FU 600 mg/m2 i.v. on Days 1 and 8) followed by 3 years of tamoxifen 20 mg daily (n = 20) or not (n = 19) - Late post-CMF treatment assessment (average of 2 years)	[18]
	- Impaired visuospatial ability - Developed fewer symptoms of depression - Impaired executive functioning	- Stage I and II breast cancer patients with no metastases (n = 28)	- Non controlled study	- Treatment with conventional (no high dose) adjuvant chemotherapy including: FAC and/or CMF and for some, Tamoxifen - 3 to 18 months adjuvant treatment within the previous 12 months and discontinuation of chemotherapy at least two weeks prior to testing	[19]
		- Survivors of breast cancer who had a history of adjuvant CMF chemotherapy treatment (n = 196)	- A case-cohort study - Control group consists of randomly chosen age-matched population-based healthy women who never diagnosed with cancer (n = 1509)	- Adjuvant CMF chemotherapy treatment (six cycles; cyclophosphamide 100 mg/m2,p.o. on days 1 through 14, MTX 40 mg/m2,i.v. on days 1 and 8, and 5-FU 600 mg/m2,i.v. on days 1 and 8) - Cognitive assessment was 20 years post-treatment	[20]
		- Early-stage breast cancer (stage I or II) currently undergoing standard-dose adjuvant chemotherapy (n = 31) or completed adjuvant chemotherapy a median of 2 years earlier (n = 40)	- The control group were healthy women (n = 36)	- Standard-dose adjuvant chemotherapy either CMF or CEF (cyclophosphamide 75 mg/m2, p.o. days 1 to 14, epirubicin 60 mg/m2 IV days 1 and 8, and 5-FU 500 mg/m2 IV days 1 and 8, cycles repeated every 4 weeks) who had received this chemotherapy for a minimum of 8 weeks (two complete cycles) - The second group had completed a full course of adjuvant chemotherapy at least 1 year ago with no clinical evidence of recurrent or metastatic breast cancer	[34]
		- Breast cancer survivors (n = 53), 2–5 years after diagnosis and initial surgical removal of cancerous tissue - 36 women has been exposed to systemic adjuvant chemotherapy with (n = 18) or without tamoxifen	- A sub-study from a larger cohort study of breast cancer women - Compared against healthy non-breast cancer subjects (n = 19)	- Systemic adjuvant chemotherapy regimens included CMF (in 41% of the women), DOX + cyclophosphamide alone or with CMF (in 38%) and the remainder receiving DOX + cyclophosphamide with taxane (in 9%)	[49]
FAC "combined therapy; antimetabolite + cytotoxic antibiotic + alkylating agent"	- Impaired memory - Impaired	- Women with non-metastatic breast carcinoma (n = 18)	- A prospective, randomized, longitudinal trial	- Treated with a standard dose of adjuvant chemotherapy	[22]

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Table 2 (*continued*)

Drug & class	Cognitive performances or impairment detection	Clinical participants	Randomization and control methods	Chemotherapeutic treatment	References
	attention - Impaired processing speed - Higher incidence of functional loss in short-term assessment (i.e., decreased ability to work)			- Pre-chemotherapy, short-term (3 weeks) and long-term cognitive assessment (1 year post-chemotherapy) were incorporated	
CEF + tamoxifen "combined therapy; alkylating agent + cytotoxic antibiotic + antimetabolite + SERM"	- Impaired memory - Impaired concentration	-High-risk breast cancer patients receiving either high-dose (n = 34) or standard-dose adjuvant therapy plus tamoxifen (n = 36)	-The patients were randomly assigned to either of the two treatment groups - Control group were composed of early stage breast cancer patients not treated with chemotherapy (n = 34) with matched age and time since therapy	- Standard-dose chemotherapy group received 4 or 5 cycles of CEF chemotherapy (cyclophosphamide 500 mg/m2 i.v.; epidoxorubicin, 90–120 mg/m2 i.v.; and 5-FU, 500 mg/m2 i.v.) - High-dose chemotherapy group consisted of 4 cycles of CEF chemotherapy and a 5th course of high-dose combination chemotherapy (cyclophosphamide, 6 g/m2 i.v.; thiotepa, 480 mg/m2 i.v.; and carboplatin, 1.6 g/m2 i.v.) - Both regimens were followed by tamoxifen treatment (40 mg p.o. once per day) for a period of 2 years	[23]
DOX + cyclophosphamide (cytotoxic antibiotic + alkylating agent)	- Impaired visuospatial skill - Impaired motor function -Impaired immediate memory and language skills	- Early-stage breast cancer patients, stages I and II (n = 30)	- A prospective, longitudinal non-controlled study	- Standard-dose of DOX+ cyclophosphamide chemotherapeutic regimen alone or followed by a taxane - Neuropsychological evaluation were performed pre-chemotherapy and after 4 cycles of DOX+ cyclophosphamide treatment	[41]
Paclitaxel (antimicrotubule)	- Induce behavioral changes - Induce confusion, hallucinations - Word finding difficulty	- A patient with advanced stage breast carcinoma with no brain metastasis, who has received surgical, radiotherapy and 6 cycles of adjuvant chemotherapy with CMF, followed by anastrazole	- A case report study	- Paclitaxel treatment (80 mg/m2, total dose 120 mg, weekly)	[67]
FAC ± paclitaxel (combined therapy; antimetabolite + cytotoxic antibiotic + alkylating agent ± antimicrotubule)	- Impaired learning - Impaired memory - Impaired executive function and processing speed	- Non-metastatic breast cancer patients with no previous chemotherapeutic treatment	- A prospective longitudinal randomized phase 3 treatment trial of breast cancer patients - Compared against published normative data from healthy controls	- Standard dose of systemic FAC chemotherapy with or without paclitaxel (n = 42) - Cognitive assessment pre-chemotherapy, during and shortly after chemotherapy, and 1 year post-chemotherapy completion	[68]

Abbreviations- SERM: selective estrogen receptor modulators; CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; MTX: Methotrexate; i.v.: Intravenously; p.o.: Per orally; FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide; 5-FU: 5-fluorouracil; CEF: cyclophosphamide, epidoxorubicin, and 5-fluorouracil; DOX: Doxorubicin.

2.2. Antimetabolites

Antimetabolites are metabolic substances which disturb the function and biosynthesis of DNA or RNA leading to cell death [13]. Methotrexate (MTX) and 5-Florouracil (5-FU)have been most frequently studied in regards to their cognitive effects either alone or their combination with other chemotherapeutic agents. In a number of animal studies, MTX has been shown to cause a variety of cognitive impairments in animals affecting spatial learning [26], Novel object recognition (NOR) [26], object placement recognition [27] and operant response learning treatment. MTX has been shown to decrease explorative behavior in rats in a variety of context [28–29]. In contrast, another study where mice were treated with a combination of MTX and 5-FU showed no impairment on a contextual fear task and novel-object recognition task (NOR) task, yet displayed increased anxiety behavior in fear conditioning and impaired auditory gating [30]. Similarly, 5-FU treatment alone impairs object placement recognition [31] and retrieval of a learned operant response in animal models [32]. In another study, a combination of MTX and 5-FU were administered to tumor-bearing mice and cognitive assessment tests were conducted before and after treatment. The results affirm their cognitive impairment effects particularly on spatial memory, learning and working memory which are functionally dependent on hippocampus and frontal lobes [33].

Regarding clinical trials (Table 2), in Breast cancer patients receiving standard-dose adjuvant chemotherapy (either, cyclophosphamide, epirubicin and 5-fluorouracil (CEF) or CMF), it was suggested that MTX component of CMF might be a cause of neurotoxicity [18]. However, no trend to any deteriorated cognitive function was observed in a different small numbered study of patients receiving CMF when compared to those receiving CEF treatment. Thus, patients receiving chemotherapy treatment were shown to have impaired cognitive deficits in the memory and language domains when compared with the healthy controls [34].

2.3. Cytotoxic antibiotics

Doxorubicin (DOX) (topoisomerase interactive agent) is the most commonly studied cytotoxic antibioticagent for its associated cognitive effects either when given alone [35–36], or in combination with cyclophosphamide [37–38]. Together with cyclophosphamide, doxorubicin showed no effect on anxiety [37], while DOX alone impaired inhibitory avoidance conditioning in rats but not passive avoidance in mice [39]. In rats, DOX and cyclophosphamide combined treatment has been shown to cause passive avoidance learning impairment [37] and in context- but not cue-specific fear memory impairment [38]. Few studies have explored chemotherapy associated mood changes in animal models, however in an acute rat study DOX was reported to induce depressive-like behaviors in forced swimming test [40].

Additionally in clinical studies, DOX has been generally associated with CICI in cancer survivors as demonstrated in a study conducted on breast cancer patients receiving DOX and cyclophosphamide, where 33% of the subjects were affected by CICI with significant decrease in visuo-spatial skills and total cognitive scores [41].

2.4. Hormonal therapy (endocrine therapy)

Hormonal therapy is a frequently used treatment approach in many cancer cases. A few studies have been conducted to examine the effect of hormonal therapy on cognition, illustrating that the occurrence and nature of cognitive impairment effects may vary between different hormonal treatments. Mostly in clinical studies, hormonal-associated cognitive effects were studied in women with breast cancer which might suggest women at a greater risk of having CICI. However, it has been stated that men are as susceptible as women for developing CICI in a small number of studies [42–44]. There is evidence that estrogen has beneficial cognitive effects and offers neuroprotection through its role in neurogenesis and synaptogenesis in the hippocampus, therefore supporting the belief of its role in CICI. While the decreased estrogen levels were found to induce cognitive dysfunction in clinical studies, contrarily it showed positive effects on learning abilities in rats [45]. In any case, CICI post-hormonal therapy has been attributed to decreased estrogen levels secondary to chemotherapy-mediated premature menopause in several studies [46–47]. Although hormonal therapy has been associated with cognitive impairment in both male and female cancer survivors [48], these findings may explain CICI in female cancer survivors while being irrelevant for male cancer survivors. Hormonal treatment with selective estrogen receptor modulators (SERMs) was found to be associated with cognitive impairment [49–50] and out of the SERMs; tamoxifen was of particular interest for study. In breast cancer women, tamoxifen has been associated with significantly impaired cognitive performances affecting memory, verbal fluency, visuo-spatial functioning, and processing speed [51], and greater cognitive impairment may be observed in those receiving both chemotherapy and tamoxifen than those treated with either alone [49]. Similarly in another study, female cancer patients receiving tamoxifen have shown more memory problems and lower writing complexity scores [52]. In mice, the antiestrogen effects of tamoxifen and toremifene were examined on selective memory aspects. It was shown that tamoxifen impaired consolidation and retrieval functions but not new memories acquisition, whereas toremifene impaired acquisition, consolidation, and retrieval more generally [53].

Another hormonal therapy approach is aromatase inhibitors, such as anastrazole, which may also contribute to cognitive impairment [54–55], although the literature is inconsistent [56–57]. Evidence suggests that the cognitive impairment associated with aromatase inhibitors may be less than those of SERMs [58]. Nonetheless, it is important to note that according to American Society of Clinical Oncology guidelines, patients are often maintained on long term endocrine treatment regimens up to 10 years [59]. Therefore, it is possible that cognitive impairment associated with endocrine therapy may emerge over time, although further studies are needed to further explore this matter.

2.5. Antimicrotubule agents

Antimicrotubule agents interfere with cell division (mitosis) and proliferation, disrupting the cell growth [13]. Among antimicrotubule agents, paclitaxeland docetaxel were found to be associated with cognitive impairment accompanied by impaired memory and learning abilities in patients and animal models [60–64]. Paclitaxel is a lipophilic agent, however it does not cross the blood brain barrier readily as it is eliminated from the CNS by an active p-glycoprotein mediated transporter system [65]. Despite poor BBB penetration, paclitaxel-induced cognitive impairment and CNS dysfunction is well documented [66]. In clinical trials, Paclitaxel-induced cognitive impairment such as behavioral changes, confusion and word finding difficultyhas been self-reported with a short 5 h onset and lasting to as long as 6 months post treatment [67]. A clinical analysis of breast cancer patients receiving a combined treatment of paclitaxel, DOX, cyclophosphamide, and 5-fluorouracil, learning and memory impairment where observed up to a year after the treatment termination confirming the paclitaxel induced cognitive deficit effects [68]. Acute and late onset paclitaxel-induced cognitive dysfunctions were observed in breast cancer patients receiving the drug [68].

However the paclitaxel-induced cognitive impairment in animal models is rather controversial. As while some animal studies displayed cognitive deficits [62–63,69–71], others do not [72]. Dose-dense paclitaxel treatment has been associated with neuronal cell death in the hippocampus and spatial memory impairment in mice [69]. In another study, there were no observed impairments in spatial and episodic memory following paclitaxel treatment in rats, yet it impaired learning of new tasks and rats failed to rapidly adapt to new experimental

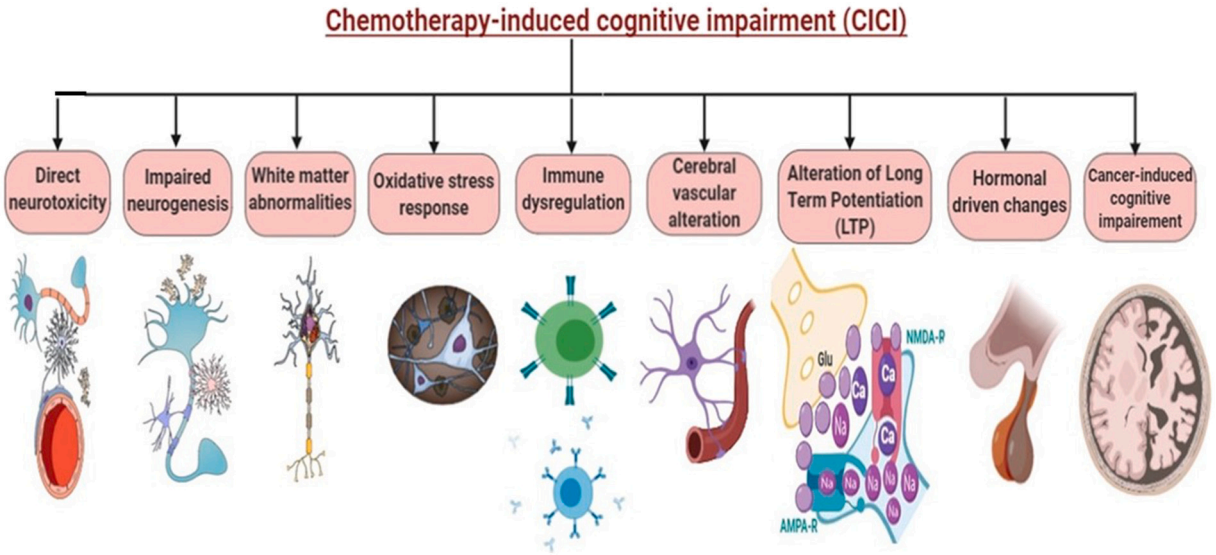

Fig. 1. Mechanisms of chemotherapy-induced cognitive impairment (CICI).

contingencies, suggesting that paclitaxel does not affect all forms of cognition [70].

Docetaxel has also been associated with cognitive dysfunction as reported in a study exploring short and long-term effects of docetaxel different dosing schedules, where NOR impairment has been observed regardless of the treatment regimen causing cognitive impairment in rats [63]. Additionally, while docetaxel was reported to impair hippocampal-dependent spatial memory, it did not impair perirhinal cortex-dependent recognition memory and it induced depressive-like behavior up to 8 weeks in forced swimming test (FST) but did not alter anxiety-like behavior in open field exploration task, suggesting long term cognitive impairment and mood changes in rats [62]. In partial contrast to these findings, it has been reported that docetaxel receiving rats showed short-term with no long-term impairment of recognition memory [63]. In a number of studies, it has been reported that docetaxel impair several cognitive functions such as; hippocampal-dependent spatial memory, perirhinal cortex-dependent recognition memory, novel object recognition and contextual fear conditioning behaviors in animal models [63–64,73].

2.6. Monoclonal antibodies

Trastuzumab (TZB) (Roche, Boston, MA, USA) is the first humanized monoclonal antibody (mAb) approved for immunotherapy and the first oncogene-targeted treatment with a proven survival benefit in HER2 positive cancer [74]. Baselga et al. revealed that TZB induces chemobrain in animal model through decreasing cerebral glucose metabolismin the region of the bilateral frontal lobe [75]. However, cognitive impairment after TZB therapy is not fully examined till now. Rituximab (Genentech, Inc., USA) is a chimeric monoclonal antibody which was approved for treatment of Non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), Rheumatoid arthritis, Granulomatosis with polyangiitis and microscopic polyangiitis and Pemphigus vulgaris. Khan et al. and Zimmer et al. showed that patients treated with Rituximab have high or elevated level of pro-inflammatory cytokines (IL-6 & IL-1β) with decreased cognitive impairment than other patients who didn't receive Rituximab [76–77].

2.7. Checkpoint inhibitor immunotherapy

Immune checkpoint inhibitors (ICIs) are a type of immunotherapy used in cancer treatment. ICIs mainly target cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed cell death 1 (PD1) or programmed cell death ligand 1 (PD-L1) to control tumor growth through activation of immune system and increasing pro-inflammatory cytokines/profile or environment and consequently elevate immune infiltrates inside or within tumor cells [78]. ICIs are better tolerated inside human body than chemotherapy [79]. However, ICIs have a better effect in cancer treatment and they increase or enhance overall survival, they cause neurological adverse events (nAEs) or immune-related adverse events (irAEs) that mimic or resemble auto-immuneconditions [80]. These adverse events include cognitive impairments (memory and concentrating deficits), behavioral alterations (fatigue, anxiety and depression) and haematological immune-related adverse events (Haem-irAEs) that may have a major impact or effect on patient's quality of life [81–83]. Theses adverse events are related to alteration in immune environment in CNS as ICIs can pass BBB or its peripheral immune activation may be sufficient to trigger or stimulate central immune response [78]. However, clinical trials showed that there is no difference in safety profile between anti-PD-1 and anti-CTLA4 treatment, howeverthe incidence of nAEs in anti-PD-1 was higher than anti-CTLA4 [84–85]. Thus, neuroinflammation and microglial activation may have a crucial rule in cognitive impairments and behavioral alterations [86–88].

3. Etiology and pathogenesisof chemobrain

The specific pathophysiological mechanisms underlying CICI are not well defined. However with the aid of preclinical animal studies and advanced neuroimaging techniques, a number of possible underlying mechanisms have been proposed at a variety of levels as illustrated in Fig. 1. These hypothesized mechanisms include direct neurotoxic effects, BBB disruption, decreased hippocampal neurogenesis, neuronal proliferation disruption and apoptosis, white matter abnormalities, secondary inflammatory response, increased oxidative stress [89], and brain blood flow alterations [90–91], among others. In addition, neurochemical changes manifested in neurotransmitters levels alteration [28], changes in metabolism, and hormonal driven changes [92] are other potential underlying mechanisms [91,93–98]. Chemobrain etiology has been postulated to be multifactorial leading to cognitive impairment through interaction of several mechanisms, since it's unlikely that a single mechanism can be considered the cause of chemobrain [92]. Here we will overview some of the most possible suggested mechanisms underlying CICI.

3.1. Direct neurotoxic effects

Central nervous system is naturally protected against any possible foreign agents by BBB, restricting several drugs penetration which might otherwise accumulate, by means of various efflux transporters such as P-glycoprotein (ABCB1). Therefore, drugs might be able to penetrate the brain, through passive diffusion if they are lipophilic enough, and/or the use of an inward directed transport system and escaping the CNS efflux transporters. However, it was found that some drugs not fulfilling these criteria may penetrate and accumulate in the brain to some extent, causing cognitive impairment even at low concentration [48,99]. Chemotherapeutic agents were thought not able to widely penetrate the BBB. However, several studies proved otherwise as some commonly used conventional chemotherapy can penetrate BBB associated with higher concentrations in brain tissue and cerebrospinal fluid (CSF) than initially expected such as 5-FU [100].

These chemotherapeutic agents can exert direct neurotoxic injury to the CNS which has been proposed to be one of the contributing etiologies of CICI. These drugs have been shown to injure the cerebral parenchyma, including the microglia, neuronal axons, and oligodendrocytes with subsequent demyelination and neurotransmitter levels alteration. Specifically, several chemotherapeutic agents when administered systemically to mice showed preferentially toxic effects on CNS progenitor cells and oligodendrocytes, associated with elevated cell death and decreased cell division in the hippocampal dentate gyrus, the corpus callosum, and the subventricular zone, such as cisplatin,carmustine, cytarabine, cytosine arabinoside [101] and 5-FU, with the later causing delayed myelin damage [93,102]. These findings were observed within the normal concentration ranges used in cancer chemotherapy, suggesting that any given dose sufficient enough to damage cancer cells could also damage normal neuronal cells in the CNS [103]. These observations might explain the delayed and long-term neurotoxic cognitive impairment effects in cancer survivors serving as a potential underlying mechanism of CICI [102].

3.2. Impaired neurogenesis

Several chemotherapeutic agents have been shown to be associated with decreased neurogenesis and/or hippocampal cell proliferation such as carmustine [102], cisplatin [102], MTX [26,104], cyclophosphamide [17], thiotepa [24–25], and 5-FU [31,93]. These findings are consistent with the observed increase in the hippocampal cell death in animals treated with carmustine, cisplatin, and 5-FU, and supporting the reported interference of chemotherapeutic agents with hippocampal neurogenesis in several studies [26,96,105–107]. Similarly, several studies have established a direct relationship between decreased neurogenesis and CICI, especially on hippocampal dependent tasks [31,106–110]. In contrast to these findings, other studies reported that hippocampal neurogenesis only have a partial or no effect on cognitive behavior as learning and memory [111–116]. Therefore, other pathophysiological mechanisms are more likely to be involved in CICI such as apoptosis, compatible with clinical studies reporting cognitive impairment to be mostly noticed in non-hippocampal dependent tasks [48].

3.3. White matter abnormalities

Reduced white matter integrity is hypothesized as a potential important mechanism underlying chemo brain [93,117]. Studies have shown white matter abnormalities and progressive damage to white matter tracts in breast cancer patients treated with adjuvant chemotherapy, which is related to CICI experienced by patients [118–120]. These white matter abnormalities have been observed within months up to 10 years post treatment, both after standard-dose and high dose treatment regimens [121–123], with reduced white matter compared to breast cancer patients who never received chemotherapy [120,124]. 5-FU was found to be associated with decreased myelin sheath and Olig2 expression deregulation, which is essential for generating functional oligodendrocytes, in the corpus callosum of rats [93]. In several studies, MTX has been associated with white matter degeneration, necrosis [125] and reduced thickness of the lateral corpus callosum [104]. Similarly, cancer patients receiving standard-dose anthracycline-based regimens showed decreased frontal and temporal white matter and in the corpus callosum genu compared to healthy and breast cancer controls [118].

3.4. Oxidative stress effects

Oxidative stress has been highly proposed as a potential underlying mechanism of CICI pathogenesis [48,126], which is mainly caused by an imbalance between reactive oxygen species (ROS) production, including free radicles and peroxides, and the biological system's antioxidant defense mechanisms. Since the effects of ROS production are represented by damage on DNA with mutations in mitochondrial DNA [127], several studies support that chemotherapy can cause DNA damage and reduced antioxidant capacity affecting the CNS secondary to increased oxidative stress, eventually leading to cognitive impairment [48,128]. In addition, it has been proposed that the increased oxidative stress byproducts associated with chemotherapy can induce cumulative damage to the CNS blood vessels, due to blood clot formation, and interfere with blood perfusion to small blood vessels in the CNS, thus attributing in CICI effects [89]. In fact, Chemotherapy associated oxidative stress has been shown in several studies for a number of chemotherapeutic agents, including cyclophosphamide [129], carboplatin [130–132], doxorubicin [133–136], cytarabine [130,137–138], carmustine [139] and MTX [140–141]. Based on these finding, several approaches are studying the concomitant use of antioxidant agents as an attempt to attenuate the oxidative stress underlying CICI. Interestingly, it has been found that CICI of cyclophosphamide and doxorubicin were absent in a study performed on rats when co-treated with an antioxidant agent [15]. This finding suggests that oxidative stress plays a vital role in the development of CICI with these used agents (cyclophosphamide and doxorubicin) and possibly the same outcome may be evident with other chemotherapeutics that cause oxidative stress, hence the use of antioxidant agents may be a possible way to overcome this adverse effect [136].

3.5. Immune dysregulation (inflammatory response effects)

One of the potentially proposed pathogenesis of CICI is immune dysregulation, with the release of pro-inflammatory mediators responsible for the inflammatory response secondary to chemotherapeutic treatment and/or the cancer. Chemotherapy associated release of inflammatory cytokines in the periphery that can cross BBB such as, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1 and IL-6 among others, is proposed to be a major contributing cause of the deteriorating effects and CICI in the CNS [142–143]. These mediators can exert their deteriorating effects in CNS through induction of central inflammatory cytokine release which can activate microglia [144–145], possibly leading to neuroinflammation [136,146] with subsequent negative effects on neurogenesis [147–148] and changes in myelination process [149], eventually manifested as cognitive impairment. This inflammatory response is mostly observed in patients treated with immunotherapies such as IL-2 and interferon-a and also with other conventional chemotherapeutic treatment such as taxanes, which has been associated with elevated levels of IL-6, IL-8, and IL-10 [150], CMF combined treatment with associated increase in IL-1β and TNF-α [97], Doxorubicin based treatment with associated increase in TNF-α [136,151–153], IL-1β and IL-6 [136,152,154]. Moreover, DOX-induced chemobrain through alteration of neuronal homoeostasis resulting in elevation of TNF-α, TGFβ, IL-17 which leads to neuroinflammation [155]. This neuronal alteration produced reduction in mitochondria oxidation (MnSOD, UCP2), mitophagy (PINK-1, Parkin) and autophagy

(LC3-II) signaling pathways [155]. However, this indirect route of CICI, which may lead to neuroinflammation process via peripheral cytokines, has hardly been explored and further studies are needed to clarify this aspect. Of interest, some clinical studies showed inflammatory neurotoxic cytokine response occurring during the development and progression of different cancer forms which could manifest even prior to chemotherapeutic treatment [156–158]. Therefore, whether chemotherapy affected the overall cytokine production on its own or the cancer progression attributed to it, is still rather unclear with little understanding of the underlying mechanisms.

3.6. Cerebro-vascular alteration

Disruption of cerebral blood flow and blood vessel density is another suggested mechanism that can result in altered neuronal functioning and lead to CICI [159]. It has been established that chemotherapy reduces cerebral blood flow and disrupts cerebral glucose metabolism [160], in clinical studies [103] as well as in animal studies, which can be attributed to the anti-angiogenic effects and vascular toxicities of some chemotherapeutic agents [159]. Similar results were observed with MTX showing decreased blood vessel density in the hippocampus [160]. Interestingly, Angiogenesis and neurogenesis are closely related [161], which led to the assumption that chemotherapy-induced cerebral blood vessel density reduction with the subsequent energy and proliferative signals depletion could be a contributing cause of the observed reduction in hippocampal cell proliferation as proposed in many studies [24,26,31,93,102,104].

3.7. Alteration in long term potentiation (LTP)

As aforementioned, numerous studies were performed to assess chemo-brain through clinical (evaluation of cognitive function) and preclinical stages (investigate the potential neurotoxic effect of chemotherapy). Neurodegeneration has not been the only signor background of chemo-brain, there is anomalous neuronal signaling and altered LTP as well. The major regulators of LTP pathway are *N*-methyl-D aspartate receptor (NMDA), a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), Ca2 + /calmodulin dependent protein kinase II (CaMKII), protein kinase A (PKA), CREB-binding protein, and extracellular signal–regulated kinase (ERK) off target proteins [162]. Sometimes, chemotherapy may not be virulent enough to cause neurodegeneration but harmful enough to decline default functions of neurons. Occurrence of LTP was represented in Fig. 2. The aim of drug targeting of LTP is shown through its importance in supporting learning and memory. In alignment with this, Fahimet al. performed computational assessment of drugs interactions with their major off-target proteins involved in neuronal LTP pathway. By using docking algorithm, their interaction may provide useful insights into functional alteration which can be related to cognitive processes [163]. Different chemotherapeutic agents were used in this study and were selected from National Cancer Institute (NCI) directory. This study revealed the top complexes which were interacting with different types of proteins, For instance, for NMDA protein: Dactinomycin, Temsirolimus, Everolimus, Docetaxel andTeniposide were selected for their potential higher interaction. For AMPA protein, Dactinomycin, Temsirolimus, Paclitaxel, Vincristine, and Irinotecan were chosen. For PKA protein, Dactinomycin, Temsirolimus, Everolimus, Docetaxel, and Bromocriptine were selected. For CaMKII protein, Irinotecan, Bromocriptine, Dasatinib, Afatinib, and Imatinib were chosen. For ERK protein, Dactinomycin, Bromocriptine, Temsirolimus, Everolimus, and Docetaxel were selected. However, further studies are yet required to identify the type of this interaction as being inhibitory or stimulatory to chemo-brain development.

These drugs could alter and modulate the induction and maintenance of LTP. In addition, this methodology could be used in studying drug repurposing and prediction of drug side effects or toxicology. Furthermore, Yang et al., proved that Everolimus as antineoplastic chemotherapy drug has a better activity in mitigating or attenuating neuroinflammation in kainic acid-induced seizures through inhibition of ERK phosphorylation [164]. In addition, Russo et al. proved that Everolimus enhances memory and learning in animal model of depression [165]. Also, Jiang et al. showed that Temsirolimus chemotherapeutic drug (mTOR inhibitor) enhance sautophagic clearance of amyloid-β and promotes protective effect in cellular and animal models of Alzheimer's disease [166]. Furthermore, it was proven that Temsirolimus has neuroprotective effects in Animal Models of Parkinson's Disease [167]. On the other hand, Bromocriptine was used in Parkinson's disease and after that used for cancer therapy [168–169]. However, more studies will be needed to clarify the agonistic and antagonistic effects of chemotherapy on LTP pathway.

3.8. Hormonal driven changes

Chemotherapy associated hormonal driven changes subsequent to chemotherapy-induced menopause has been found to negatively affect cognitive functions, thereby serves as a contributing mechanism to CICI observed in cancer patients [48,170]. A number of trials highlighted the neuroprotective and antioxidant effects of both estrogen and testosterone hormones [48,171], hence support the hypothesis that a reduction in these hormones concentrations secondary to hormonal anticancer therapy can lead to CICI. This hormonal therapy- induced cognitive impairment has been reported mostly in breast and prostate cancer patients even when given as monotherapy without chemotherapy, which may occur following the start of hormone therapy due to decreased estrogen and testosterone levels [48].

CICI has been observed in cancer patients treated with hormonal therapy most commonly with, aromatase inhibitors, tamoxifen or androgens [172]. Several studies reported the anti-estrogen effects of tamoxifen on cognitive performance in cancer patients [173] with similar findings observed with tamoxifen and toremifene in mice [53]. Similarly, Cognitive impairment has been associated with thyroid hormone replacement therapy after thyroidectomy following thyroid carcinoma due to the possible influence of thyroid hormone on mood and cognition [174–175]. However, some literature contains conflicting data due to methodological bias and the studies heterogeneity [176–178]. In a study of 110 breast cancer patients, there was no significant evidence supporting the hormonally mediated mechanism causing cognitive impairment after administration of adjuvant chemotherapy [61]. Therefore, further investigations are required to fully explore the effects of hormonal anti-cancer therapy on the cognitive functions of cancer survivors using both animal models and more detailed neuropsychological testing in selected test subjects.

3.9. The biology of cancer itself effect (cancer-induced cognitive impairment)

The biology of cancer itself has been found to be a possible contributing etiological factor of the cognitive impairment observed in cancer patients. This hypothesis was suggested based on the studies reporting signs of cognitive impairment after cancer diagnosis and before the onset of chemotherapeutic treatment [179–181]. In animal studies, the presence of a tumor has been accompanied by hippocampal dysfunction, presumably due to the decreased rate of hippocampal neurogenesis [182], the increased levels of pro-inflammatory cytokines and stress-related parameters, as well as the reduced levels of cyclooxygenase 2 (COX-2) and brain-derived neurotrophic factor (BDNF) [183]. Furthermore, in cancer patients the observed early cognitive impairment can be attributed to emotional stress following cancer diagnosis [184], systematic inflammatory response triggering neuroinflammatory cascades, or an underlying risk factor for cognitive decline and cancer development such as, deficient DNA repairing mechanisms that is linked to neurodegenerative disorders and cancer development

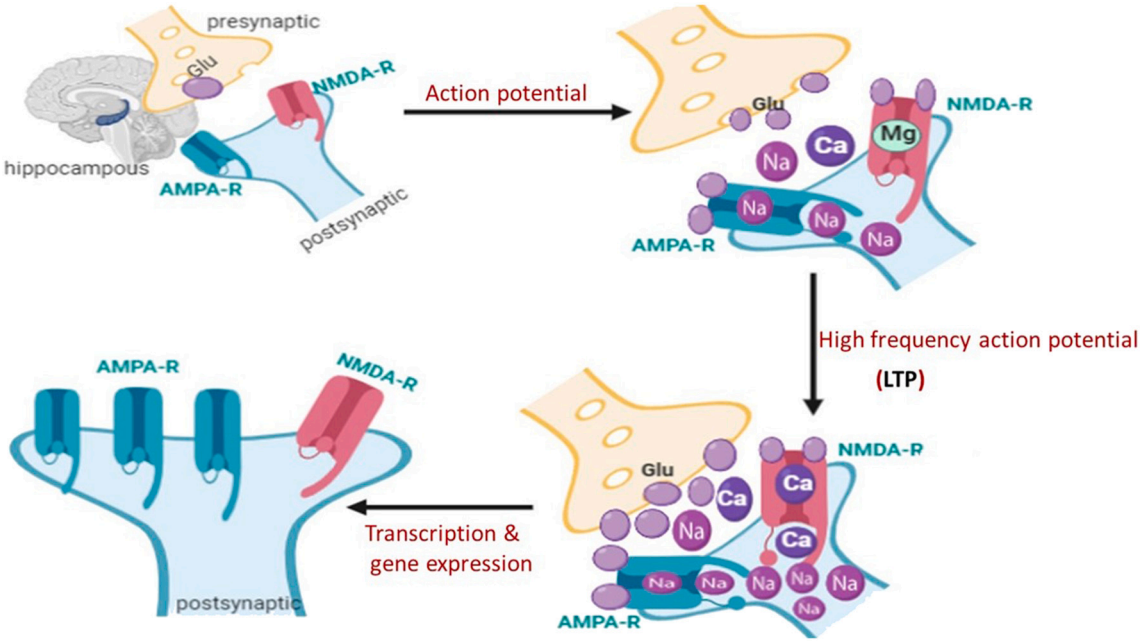

Fig. 2. Mechanism of long term potentiation (LTP).
LTP is one of the major cellular mechanisms that underlie learning and memory. LTP is persistent strengthening of synapses based on recent patterns of activity. Hippocampus is responsible for storage and retrieval memories. As LTP is a long lasting enhancement of signal transmission As LTP is a long lasting enhancement of signal transmission between two neurons after repeated stimulation, Presynaptic neurons secrete glutamate that stimulates postsynaptic neurons through AMPA-receptor and NMDA-receptor. AMPA-R is permeable to Sodium (Na) and NMDA-R is permeable to Na but it has higher permeability to Calcium (Ca) and it is blocked by magnesium (Mg). When action potential travels or occurs, glutamate will be released and bind with AMPA-R then Na enters neurons. However, glutamate binds with NMDA-R also, there is no entrance of Na due to blockage by Mg. in case of high frequency action potential; large amount of glutamate are released in synaptic terminal then binds with AMPA-R to generate depolarization for long time results in increase in Na influx that with binding of glutamate and NMDA-R cause large depolarization in postsynaptic cell/neuron and allow influx of Ca/Na. Ca influx acts as 2^{ry} messenger that activates many 2^{ry} intracellular cascade. In early phase of LTP, Ca binds to certain binding protein results in increase AMPA-R but last only for few hours. In late-LTP, prolonged influx of Ca causes increase in transcription factor that lead to gene expression and synthesis of new proteins such as AMPA-R inserted in postsynaptic neurons.

[48,91,179–181].

Cancer-related anemia, which is a very common adverse effect of cancer and/or chemotherapy, has been suggested as another possible factor inducing several deteriorating symptoms such as, cognitive impairment and impaired executive function tasks and visual memory by decreasing cerebral oxygenation [185]. Several studies have been conducted so far investigating the effect of epoetin-alpha (Ea) on the cognitive functions of cancer patients, showing potentially promising yet indecisive results [186–187]. In fact, this may justify the emerged belief that Ea may not only enhance cognitive performance but also prevent cognitive impairment in breast cancer patients undergoing adjuvant and neoadjuvant anthracycline-based chemotherapy. On the contrary, in another study although Ea corrected anemia over time, there were no significant subjective or objective changes in the patient's cognitive functions over a period of 12 weeks [188]. Furthermore, there was no significant memory impairment or brain volume changes observed, which appear to be an important factor in CICI, in breast cancer survivors who had taken adjuvant chemotherapy compared to those who had not [189]. Despite some limitations in that study such as the difference of memory impairment measurement and the long interval between the adjuvant chemotherapy and the hippocampal measurements, exceeding 3 years, which might allow recovery for some chemotherapy-induced adverse effects, the absence of chemotherapy-induced memory impairment should be taken into consideration. Interestingly, some investigators reported chemotherapy-induced brain shrinkage in cognitive functions-related areas in cancer survivors receiving adjuvant chemotherapy, which was not observed at more than 3 years after completion of chemotherapy [123].

In summary, to some extent chemotherapy can be the attributing factor of cancer-related cognitive impairment observed in patients treated with chemotherapy; however it cannot explain all cases as it fails to be accounted for the cognitive impairment observed in patients not receiving chemotherapy. Nevertheless, many of the factors mentioned above have a critical and concomitant role in the development of cognitive impairment in cancer patients, thus more comprehensive and extensive studies are still needed to fully understand these relationships.

4. Conclusion

Multiple animal studies and clinical investigations have stated that several chemotherapeutic agents, alone or in combination, are accompanied with cognitive dysfunction referred to as CICI, particularly in the hippocampal domains of memory, learning and executive functions. These observed cognitive impairment widely vary, with mild to severe manifestations, and rapid recovery in some cases or long lasting for long periods after chemotherapy cessation in others, hence impacting the overall patients' quality of life [9]. Despite the growing body of research investigating CICI, there is still indefinite understanding possibly attributed to some inconsistencies across the literature in the methodologies, the study findings and even in the used definition of cognitive impairment. Similarly, the pathophysiological mechanisms and etiologies underlying CICI is equally a point of interest being investigated widely in several researches. With most of the chemotherapeutic agents lacking the ability to cross BBB, several mechanisms have been hypothesized to explain the observed CICI in cancer survivors. Among the postulated mechanisms, direct neurotoxicity, BBB disruption, reduced hippocampal neurogenesis, secondary neuroinflammatory/immune responses, white matter abnormalities and increased oxidative stress are of great relevance being the major possible mechanisms explaining CICI. A schematic illustration of the most common chemotherapeutic agents involved or participating in

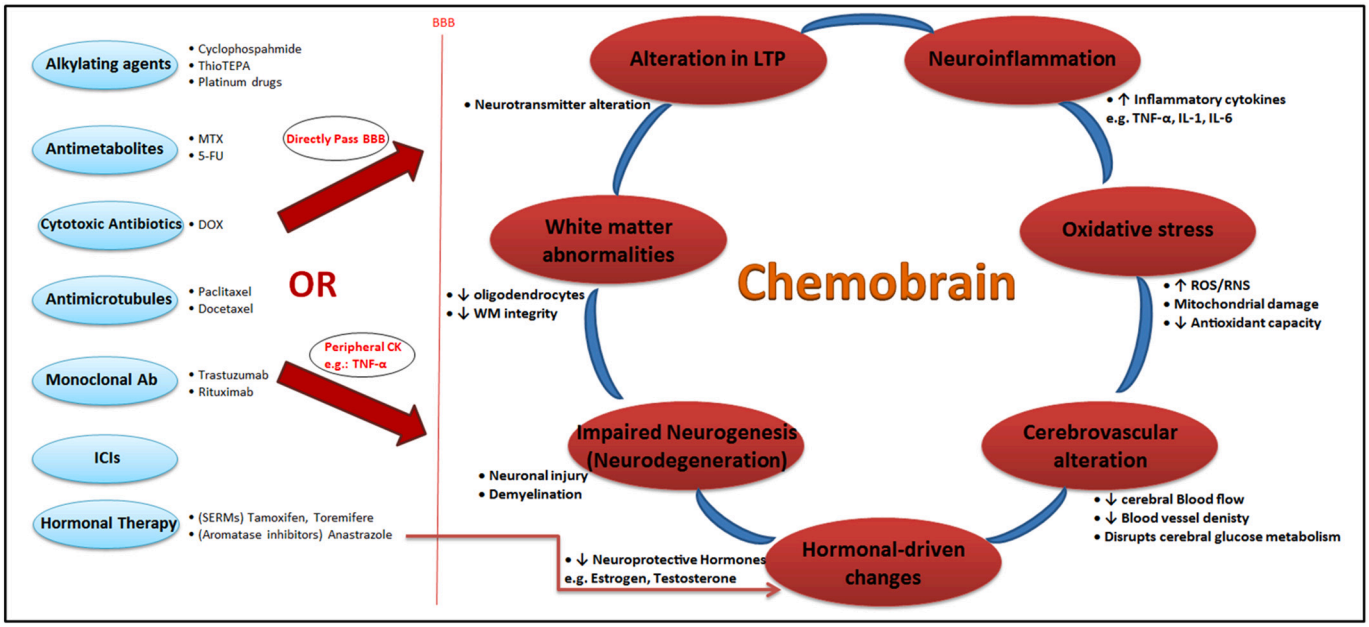

Fig. 3. A schematic illustration of the most common chemotherapeutic agents involved or participating in chemobrain pathogenesis.
MTX: Methotrexate; 5-FU: 5-fluorouracil; DOX: Doxorubicin; ICIs: Immune checkpoint inhibitors; SERMs: selective estrogen receptor modulators; CK: Cytokines; TNF-α: Tumor necrosis factor-alpha; LTP: long term potentiation; ROS/RNS: Reactive oxygen species/Reactive nitrogen species; WM: White matter.

chemobrain is depicted in Fig. 3. Additionally, some investigations observed cognitive deficits post diagnosis and prior to any systemic chemotherapy treatment, suggesting the biology of cancer itself with its associated inflammatory cascades and the stress-related parameters to be a significant factor in cognitive impairment. In any way, these mechanisms are not mutually exclusive and several factors could be linked and contribute to the CICI. In summary, CICI is a rather complicated process with very limited decisive data fully explaining its occurrence, and with multifactorial pathogenesis with the interaction of several mechanisms inducing cognitive impairment. Further comprehensive and detailed studies to fully explain CICI and provide a clear understanding of its etiologies and pathogenesis, are needed in both clinical and animal models.

Research involving human participants and/or animals

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Declaration of competing interest

The authors declare that they have no conflicts of interest.

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