Oxidative stress, brain and chemotherapy

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Preclinical evidence shows that several chemotherapeutic drugs widely used in cancer patients such as anthracyclines, taxanes, and platinum derivatives induced oxidative stress noted in the blood and brain, which may affect both neurons and glia cells. In animal models, the oxidative stress induced by chemotherapeutic drugs is accompanied by cognitive deficits. Administration of several antioxidants decreased or prevented these effects and helped pinpoint the potential role of antioxidants as drugs that may be able to reduce both oxidative stress and cognitive dysfunction caused by chemotherapy.

Keywords: taxanes ; anthracyclines ; platinum ; cognition ; biomarker ; acetylcysteine ; clinical trial

1. Introduction

The study of cancer treatments currently occupies a prominent place in research and public health policies. These focus not only on curative or palliative purposes, but also on reducing the toxicity of cancer treatments which can, in turn, increase adherence to oncology protocols and improve quality of life and survival [1][2][3]. Antineoplastic therapies entail multiple side effects and must be closely monitored to promote better assimilation of the treatment as well as to encourage patient adherence to chemotherapy regimens and mitigate reductions in their quality of life. Chemotherapy is currently one of the most important tools in the fight against cancer; many of its side effects are well known, however, others such as cognitive impairment are still being studied.

Cognitive impairment appears in up to 50–75% of people who undergo chemotherapy [4][5]. Some cancer patients report difficulties in concentration, memory, and attention both during and after the process of treating the disease, referred colloquially as ‘chemofog’ or ‘chemobrain’. Although in most cases the damage may be subtle and temporary, in a subgroup of patients, these alterations are more severe and can persist for years [6][7]. However, it should be borne in mind that even a subtle cognitive deterioration can have substantial repercussions on daily life [8][9]. Several factors such as the combination of cancer treatments, dose used, administration route, previous genetic vulnerability, and some psycho-social characteristics, among others, could give rise to these individual differences. However, chemotherapy drugs such as doxorubicin, cisplatin, 5-fluorouracil, methotrexate, and other anti-neoplastic agents trigger cognitive dysfunction in many patients [10][11][12][13][14]. These drugs are widely used in cancer chemotherapy to treat many cancers, including lymphoma, sarcoma, breast cancer, and many pediatric cancers [15][16]. About one third of women with breast cancer and half of children with cancer are treated with anthracyclines, including doxorubicin and epirubicin, and the class of taxanes, which includes paclitaxel among other drugs that are commonly used [17][18].

Oxidative stress is a dynamic and complex condition characterised by an imbalance between the generation of reactive oxygen species (ROS) and the availability and action of antioxidants [19][20][21]. The central nervous system consumes large amounts of oxygen to carry out physiological processes, leading to elevated free radical generation [22][23]. Some factors make the CNS susceptible to ROS attack, such as the deficit of antioxidant mechanisms, presence of high levels of polyunsaturated fatty acids, and selectivity of the blood-brain barrier, which reduces the diffusion of some antioxidants [23][24]. The escape of ROS from antioxidant mechanisms and their progressive accumulation trigger lipid peroxidation mechanisms as well as structural damage to proteins and DNA [25].

Oxidative stress is a factor in several neurodegenerative diseases, including Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis [26][27][28] and is also thought to be a cornerstone of the pathophysiological mechanisms of drug-induced damage in several organs and tissues [29][30][31][32]. Indeed, several reports have shown that several pathophysiological factors lead to cognitive impairment after chemotherapy administration [33][34][35][36]. For instance, an increase in inflammatory markers in blood leading to their entry into the brain, white matter alterations, impaired neurogenesis, and cerebrovascular alterations have all have been proposed as possible factors that contribute to cognitive impairment. Moreover, both in vivo data obtained in animal models and in vitro experiments in cultured cells suggest that chemotherapy produces both an increase in oxidative stress and a decrease in antioxidative enzymes.

2. Neuronal and Glial Oxidative Stress Induced by Chemotherapeutic Drugs in Preclinical Studies

Compared to in vivo studies, relatively few in vitro studies have investigated the direct effects of anticancer drugs on neurons [37][38][39]. In primary cultures of rat neural stem cells or progenitor cells and hippocampal neurons, cisplatin and temozolomide induced mitochondrial DNA damage, impaired respiratory activity, and increased oxidative stress [38][39]. However, the presence of antioxidants in the culture medium used in cell culture experiments may be sufficient to block the effect of anticancer drugs and therefore, these systems are not suitable for examining ROS-mediated neurotoxicity because they may not reflect the actual conditions of chemotherapy-treated animal models or patients.

Thus, to mimic the in vivo conditions of chemotherapy, an elegant study showed that methotrexate, 5-fluorouracil, or cisplatin neurotoxicity only occurred when primary cell cultures obtained from the cortical and striatal neurons from rat embryos were incubated with low concentrations of antioxidant substances [37][40]. Furthermore, the co-administration of methotrexate and 5-fluorouracil through incubation, as assessed with a cell-permeable fluorogenic probe (DHR123), showed a significant increase in intra-mitochondrial ROS. Together, these data indicate that oxidative stress plays a fundamental role in the mediation of in vitro neuronal toxicity. In other work, a far-red photostable fluorogenic probe (CellROX Deep Red Reagent) was used in primary cultures of rat hippocampal neurons to show that ROS was not increased by cyclophosphamide but that exposure to doxorubicin led to a 3-fold increase in CellROX signal intensities [41]. These data suggest that neurotoxicity is drug-dependent, and the main mechanism of chemotherapy-related cognitive impairment is unlikely to be increased oxidative stress.

In addition to mitochondria, peroxisomes also generate ROS, which in turn, promote cell senescence [42][43]. These ubiquitous cytoplasmic organelles are single-membrane vesicles that are found in most eukaryotic cells [44]. Peroxisomes are oxidative organelles in which molecular oxygen acts as a co-substrate for the formation of hydrogen peroxide. Of note, the anthracycline derivative, doxorubicin, affects peroxisomal homeostasis in neurons [45]. Moreover, in an H 2O 2 environment, the level of oxidative stress was enhanced in neurons [46] and primary cultured doxorubicin-treated neurons from rat embryos displayed an increase in oxidative stress in peroxisomes [47]. Besides neurons, some chemotherapeutic drugs have been shown to promote oxidative stress in glia cells [48]. In cultures of primary rat astrocytes, oxaliplatin induced an increase in superoxide anion production up to 10-fold compared to the controls and also induced the oxidation of lipids, proteins, and DNA [48][49]. Indeed, the level of protein carbonylation was approximately doubled in oxaliplatin-treated cells compared to control samples. Furthermore, in astrocyte cultures, the basal concentration of the oxidative stress marker 8-OH-dG also increased up to 9-fold after incubation with oxaliplatin [48]. Oxidative stress is often reported to be accompanied by DNA damage. For instance in primary neurons, the anthracycline doxorubicin, promotes the formation of DNA double-strand breaks and reduced synaptic and neurite density [50].

3. Treatment to Prevent Oxidative Stress and Cognitive Dysfunction Induced In Vivo by Chemotherapeutic Drugs

Different in vitro studies in neuronal and glia cell cultures have demonstrated that the oxidative stress induced by exposure to the chemotherapeutic drugs used in cancer treatment is reduced by molecules with antioxidant properties, as summarised in **Table 1** [48][49][51][52][53]. However, treatment with acetyl-carnitine, which has been shown to decrease the ROS formation induced by doxorubicin exposure to neurons in vitro [54], has not been tested in vivo in animal models. Co-administration of different antioxidant compounds in animal models reduced oxidative stress levels and improved the cognitive deficits elicited by the administration of chemotherapeutic drugs [55][51][56][57][58][59][60].

Table 1. Drugs proven to decrease both the oxidative stress and cognitive dysfunction induced by the administration of chemotherapeutic drugs in animal models.

Antioxidant Compound	Drug-Induced Cognitive Impairment and Oxidative Stress	Behavioural Test Used to Assess Cognitive Function
***N*-acetylcysteine [88]**	**Cisplatin**	**Recognition memory task** **Fear conditioning learning** **Object discrimination**
***N*-acetylcysteine [54]**	**Doxorubicin**	**Recognition memory task**
Cyclophosphamide		

Antioxidant Compound	Drug-Induced Cognitive Impairment and Oxidative Stress	Behavioural Test Used to Assess Cognitive Function
Gamma-glutamyl cysteine ethyl ester [89]	Adriamycin	Recognition memory task
Polydatin [56]	Doxorubicin	Morris water-maze task Step-down avoidance task
Caffeic acid phenethyl ester [57]	Doxorubicin	Passive avoidance test Morris water-maze task
MESNA [53]	Doxorubicin	Recognition memory task

MESNA, 2-mercaptoethane sulfonate sodium.

N- acetylcysteine treatment (250 mg/kg/day) prevented free radical production, ameliorated apoptotic cellular death and dendritic spine loss, and partially reversed cisplatin-induced cognitive impairments [38]. A regimen of repeated cisplatin treatment in rats led to impaired cognitive performance (contextual fear conditioning, context object discrimination, and novel object recognition tasks), but this effect was partially mitigated by concomitant N- acetylcysteine treatment [59]. Moreover, administration of gamma-glutamyl cysteine ethyl ester, a glutathione precursor (150 mg/kg) prior to adriamycin administration (20 mg/kg body weight) led to a decreased production of protein oxidation and lipid peroxidation [60]. Furthermore, N- acetylcysteine reversed the anxiety-like behaviour and recognition memory task inhibition induced by doxorubicin and cyclophosphamide in rats [56]; this effect was also accompanied by a parallel improvement in the rats' hippocampal GSH/GSSG ratios [56].

Polydatin, a resveratrol glycoside and potent natural antioxidant [61] extracted from the root of Polygonum cuspidatum, also counteracted the effect of the anthracycline drug doxorubicin. Prior treatment with polydatin inhibited doxorubicin-induced cognitive deficits in rats, both at the neurobehavioral and hippocampal histopathological levels [57]. Administration of caffeic acid phenethyl ester, a natural polyphenolic compound that exhibits unique context-dependent antioxidant activity was also able to counteract behavioural impairment and oxidative stress in hippocampal and prefrontal cortical tissues in rats treated with doxorubicin, as measured by the reduced glutathione content and malondialdehyde concentration in these brain areas [58].

Finally, administration of the antioxidant drug 2-mercaptoethane sulfonate sodium (MESNA) improved the production of oxidative stress markers in the blood and brains of rats treated with doxorubicin (determined using protein carbonyl and protein-bound 4-hydroxy-2-nonenal as indicators of protein oxidation and lipid peroxidation, respectively) [51][52]. In parallel, MESNA administration prevented the memory deficits induced by doxorubicin in the object recognition task [51]. These latter results are very promising for future clinical trials because MESNA is already being used in oncology patients to prevent urothelial toxicity including haemorrhagic cystitis, microhaematuria, and macrohaematuria in patients treated with chemotherapeutic drugs belonging to the oxazaphosphorine family (ifosfamide and cyclophosphamide) at doses considered to be urotoxic [62][63].

4. Oxidative Stress Markers After Chemotherapy Administration in Cancer Patients

In lung cancer patients, the concentration of the oxidative DNA damage markers 8-oxoguanine (8-oxoGua) and levels of 8-oxo-2'-deoxyguanosine (8-oxodG) in urine and whole blood were higher than in controls [64]. In addition, patients with stage IV cancer had higher urinary 8-oxoGua and 8-oxodG levels than patients with stage I–III disease. These results suggest that cancer promotes oxidative stress per se [65][66][67] and so, oxidative stress markers should be measured before chemotherapy administration in order to assess the effects of chemotherapeutic drugs versus those of the cancer alone. Urinary 8-oxodG levels have been shown to increase after radiotherapy and after six cycles of chemotherapy in lung cancer. Moreover, DNA oxidation parameters were increased both after radiotherapy and chemotherapy, suggesting that a pathophysiological mechanism such as the anti-cancer effects of these drugs may underlie these effects [64].

In previously untreated cancer patients (mainly with breast or endometrial tumours), Cadeddu et al. [68] evaluated various effects of the anthracycline drug epirubicin, including oxidative stress markers [68]. The levels of ROS were determined in blood samples using the free oxygen radicals test (FORT, with 1 FORT-U corresponding to the oxidative stress elicited by 0.26 mg/L of H 2O 2) [69]. In addition, they also measured the antioxidant enzyme glutathione peroxidase in red blood cells [68]. The administration of epirubicin promoted ROS formation and reduced the expression of glutathione peroxidase, suggesting that this drug induced oxidative stress.

Cisplatin-induced toxicities mainly seem to be caused by the formation of free radicals, leading to oxidative organ damage [70][71]. In fact, the plasma concentrations of the antioxidants vitamin C, E, and ceruloplasmin decreased after the administration of cisplatin or cisplatin-containing chemotherapy regimens. This appears to be a drug-induced effect because the concentrations of these substances returned to their initial levels just before the start of the next chemotherapy cycle. In addition, the levels of the antioxidants bilirubin and albumin also gradually decreased when measured just before the start of the next chemotherapy cycle. Furthermore, the copper/ceruloplasmin ratio, a marker of pro-oxidative status, significantly increased in the first cycle of cisplatin-based regimens [70]. In analogy of in vitro and in vivo studies as well as in human studies, direct DNA damage has been reported as a result of the mechanism of the action of chemotherapeutic drugs and oxidative stress. This has only been studied in lymphocytes derived from patients treated with chemotherapy. A substantial increase in both oxidative and direct DNA damage measured in the peripheral lymphocytes assessed by the Comet assay have been reported from before to shortly after chemotherapy administration in cancer patients [72][73][74][75][76].

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