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A Review: Neurotoxicity of Doxorubicin

Hanan B. Saadon*[1a] and Noor Abd Alkhudhur Salman[2b]

[1] *Department of Path. Analysis, College of Science, University of Thi-Qar, Iraq.*
[2] *Department of Chemistry, College of Science, University of Thi-Qar, Iraq.*

[b]E-mail: noor.abdulkhudur@sci.utq.edu.iq
[a*]Corresponding author: hananaljaberi@sci.utq.edu.iq

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***Abstract*— Although, Doxorubicin an effective chemotherapeutic agent, has been associated with significant neurotoxic effects, impacting the nervous system. This neurotoxicity can lead to various neurological complications, including cognitive impairments, neuropathic pain, and motor dysfunction. The neurotoxic effects of Doxorubicin are attributed to several mechanisms, including oxidative stress, inflammation, neuroinflammation and apoptosis of neuronal cells. These pathways become even more complex when multiple drugs are used simultaneously or in a fixed sequence, which is often the case in combination chemotherapy brain damage. Further research is needed to elucidate the precise mechanisms underlying doxorubicin-induced neurotoxicity and explore potential protective agents. In addition, studies focusing on long-term neurological outcomes in cancer survivors treated with doxorubicin are warranted. Developing neuroprotective agents or alternative treatment regimens or using nanocomposites that reduce the neurotoxic effects while maintaining the efficacy of doxorubicin is a very important area for future investigation.**

***Keywords*— Cytotoxicity, Doxorubicin, Neurotoxicity, Chemotherapy, Oxidative stress, Blood-brain barrier.**

I. Introduction

Chemotherapy agents are classified by mechanism, function, or chemical structure in several ways. According to mode of action, chemotherapy can be classified into five categories including alkylators, antimetabolites, topoisomerase inhibitors, mitotic spindle inhibitors and others [1-3]. Inhibitors of topoisomerase I, such as irinotecan and topotecan and inhibitors of topoisomerase II like etoposide, teniposide, anthracyclines (idarubicin, daunorubicin), doxorubicin have direct effects on DNA by producing DNA strand breaks due to changes in different types of reactions that require action of various isomerases involved in the process from replication to transcription [3]. Doxorubicin (DOX) is known to present potent therapeutic properties and it is considered to be one of the most highly powerful chemotherapeutic agents approved by Food and Drug Administration for treatment of many types of cancers including breast cancer, melanomas, sarcomas and hematological malignancies [4].

Although anthracyclines are widely used, they have multiple toxicities, including well known and extensively studied cardiotoxicity (reviewed in [5-9] . Other than these, other organs including brain [10-12] , liver [13], and kidney [14] can suffer damage in severe cases. It is well recognized that the anticancer activity of DOX can be explained by: (1) ability of the drug to intercalate into DNA, (2) its inhibitory effect on topoisomerase II, (3) disruption of mitochondrial function and (4) enhancement of free radical's production and oxidative damage [15, 16]. Anthracyclines may also have nonspecific effects in the short-term and on the functional levels of the body, the field of neurotoxicity, that maybe clinically expressed with cognitive impairment, & is related to anatomical altered structures in the brain as well as in the peripheral nerve the system identified in basic research, as well as in clinical analyses [17, 18]. The purpose of this review is to assess doxorubicin's neurotoxic effects., a commonly used chemotherapy drug, focusing on its mechanisms, effects on the nervous system, and long-term impact on patients' quality of life, emphasizing the need for further research to better understand these effects and develop strategies to reduce them.

II. Neurotoxicity of Doxorubicin

The central nervous system receives a layer of protection from the blood-brain barrier (BBB), which is thought to prevent most chemotherapeutic agents from entering [19]. Doxorubicin (DOX), which is a known substrate of the efflux pump P-glycoprotein, is well known to have little penetration into the central nervous system (CNS) as doxorubicin, its active metabolite, is not present in clinically relevant levels in the circulation after intravenous treatment. It should be noted that the toxicity and cognitive dysfunction associated with DOX may be indirect and result from toxicity of DOX at peripheral sites, or other factors, such as drugs that are capable of damaging the central nervous system. DOX produces reactive oxygen/nitrogen species through redox cycling and alters the cellular iron balance, thus causing off-target organ damage. DOX can cause oxidative damage to molecules like plasma proteins which stimulates production of proinflammatory cytokine such as TNF-α [20] that is capable of permeating through tissues and setting off local inflammation and oxidative stress [19]. The Table 1 below provides a summary of some previous studies investigating the neurotoxic effects of doxorubicin across different models and types of studies, highlighting key findings [21-25].

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Table 1: Comparison of Studies on Doxorubicin-Induced Neurotoxicity

Model used	Findings	References
3D human brain organoids	The study continues to develop cancer immunotherapies to analyze the tumor immune environment using a patient-derived 3D organ model for effective clinical cancer regimens and multi-combination therapy where safety is not an issue.	[21]
Breast cancer survivors	Persistent memory impairment after chemotherapy	[22]
Rodent models	DOX caused cognitive impairment mainly through its neurotoxic effect on the rats.	[23]
Cancer patients	Cognitive decline observed in survivors	[24]
Cellular models	DOX- induced endothelial dysfunction results in the enhanced mitochondrial ROS in conduit arteries that can be, therefore, reduced with the use of the mitochondrial-specific antioxidant.	[25]

Table 2: Mechanisms of Doxorubicin Neurotoxicity

Mechanism	Description	References
Oxidative Stress	This review provides details about the processes occurring in oxidative stress and cell death following use of Doxorubicin, an effective antineoplastic agent, and intends to provide further leads on the approaches to its treatment.	[25]
Neuroinflammation	DOX stimulates the IL 6 signaling pathway promoting IL 8, IL2, and cancer stem cells, disrupting neuronal homeostasis and causing long-term damage.	[26]
Mitochondrial Dysfunction	Impairs ATP production, increases ROS release, and triggers neuronal apoptosis through intrinsic pathways.	[27]
Apoptosis	Activates both intrinsic and extrinsic apoptotic pathways, leading to neuronal cell death and reduced brain plasticity.	[28]
Disrupted Neurogenesis	Reduces hippocampal neurogenesis, affecting cognitive function, memory, and learning.	[29]

A. Direct neurotoxicity of doxorubicin

The view of doxorubicin as a drug with a minimal ability to cross the blood-brain barrier, thus safeguarding the brain from toxicity has been the prevailing one. More recently, however, doxorubicin has been reported to have some anticancer activity against brain tumors [21]. Both clinical and preclinical studies have confirmed that doxorubicin was present within the brain after peripheral administration [22, 23]. In a recent publication, the potential of doxorubicin to traverse the blood-brain barrier by virtue of blood vessel-associated vascular protrusions of neural stem cells (30-50 nanometer) which can make a membrane-to-membrane connection with endothelial cells in the peculiarly shaped deficiency of an endothelial basement membrane and are greatly reticulated was described [24]. Table 2 below provides a summary of the main mechanisms underlying doxorubicin-induced neurotoxicity, with an emphasis on oxidative stress, neuroinflammation, mitochondrial dysfunction, apoptosis, and neurogenesis disruption.

1) Autophagic and apoptosis

Doxorubicin interferes with neuronal degradation burden, alters lysosomes, induces pre-phagosome formation, increases autophagy and influences the mechanism related to p62 protein degradation. As observed, exposed neurons have increased vacuolar structures, autophagosomes, mitochondria, and lipid droplets; which led to cognitive dysfunction following chemotherapy due to degradation disorders [40]. ROS can be produced in aerobic organisms by the electron transport chain (ETC), the functioning of catabolic oxidases, and the catabolic metabolism. peroxisomes [41]. ROS are usually involved in cell signaling in redox signaling. conditions when their concentrations are kept comparatively low [41]. Nevertheless, an excessive There is evidence that generation of ROS can lead to DNA damage through reaction of radicals on positions as the other and DNA bases and the sugar–phosphate backbone [42]. Unrepaired damage can lead to proapoptotic [43], antiproliferative [44], and pro-senescent [45-46]. Doxorubicin toxicity and apoptosis in primary cortical neurons are primarily influenced by the exogenous pathway, which is an indirect mechanism of action that triggers apoptosis. This pathway is triggered by doxorubicin, which enhances the bond between cell surface receptors Fas and FasL, recruiting a specific protein called Fas associated death domain (FADD) to trigger exogenous apoptotic signaling. Apoptosis, a process triggered by cellular stress, DNA damage, growth signals, or survival-promoting factors, is regulated by Bcl-2 family proteins and linked to mitochondrial oxidative stress. Abnormal apoptosis can decrease neuron numbers and cause cognitive dysfunction [47] as showed in Figure 1.

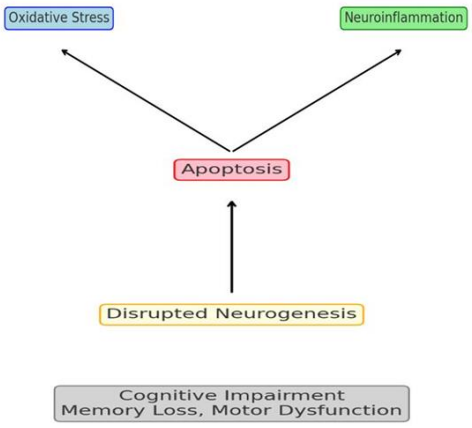

Fig. 1: Mechanisms of Doxorubicin-Induced Neurotoxicity

2) Destroyed neurogenesis

Another structure closely connected with formation / recall of memory and spatial processing is hippocampus and neurogenesis in hippocampus heavily depends on the incorporation of new neurons in the network [48]. Neurogenesis was reduced in doxorubicin treated animals evidenced by a perceptible reduction in the number of nuclear antigens BrdUrd labeled cells [49]. Others have also found that the treatment with DOX and cyclophosphamide reduced the cells survival of the dentate gyrus and subgranular layer of rats [50]. Many studies have also confirmed that doxorubicin activates the astrocytes and subsequently stimulates the release of the inflammatory signals making the nerve nonviable [24]. As stated in several studies TNF-a harms neurogenesis and is able to decrease amount of BrdUrd positive marked cells in the sub-granular zone after injection [51]. In addition, BrdUrd-labelled cells isolated from the subgranular zone of the hippocampus were found to proliferate more vigorously in the knockout mice deprived of TNF-a-receptor-1 (TNFR1), suggesting that TNFR1 underlies the antagonism of TNF- α against neurogenesis. As well as inhibition of cell survival, differentiation and division of hippocampus, neuroinflammation also prevents the addition of new neurons into existing networks [52].

3) Neurotransmitter regulation

Many experimental investigations performed on animals show that doxorubicin can cause the disturbance of neurotransmitter synthesis and release in the brain. Considering long-term potentiation (LTP) as the memory maintenance mechanism involves acetylcholine (ACH) which is neurotransmitter from the cholinergic nervous system [53]. PLD is shown to cleave into phosphatidylcholine (PtdCho) to enable synthesis of acetylcholine through the formation of choline. Thereafter the released choline is converted by choline acetyltransferase (ChAT) into acetylcholine. After doxorubicin treatment PLD, ChAT activity and choline-containing substances in the hippocampus area were significantly reduced to express that ACH synthesis has been saturated [54]. In addition, the ROS induced by doxorubicin enhanced the effect of oxidative stress on acetylcholinesterase (AChE) [55]. It has been assumed that these alterations are related to membrane turnover process, involving phospholipid synthesis and degradation, and have been related to myelin disruption following chemotherapy [27].

Tumor necrosis factor (TNF), formerly known as TNF-α has been reported to or decrease PtdCho formation by inhibiting the activity of PLD. Moreover, phosphatidic acid decrease is thought to be mediated by TNF-a, which suggest dependency between phospholipase and TNF- α expression [56]. Inhibition of PLD also leads to decreased cytokine secretion notably TNF- α level [57]. In the mouse brain, phosphatidic acid derived from the PLD pathway decreases doxorubicin-induced mitochondrial injury through the regulation of intracellular Ca2+ movement with growth factor-like effect. Cell viability is directly related to the function of PLD activity; structural changes in PLD and reduced activity lead to activations of the apoptotic pathways [58].

4) Synapses dysplasia

Neurotoxicity is prevalent in cancer survivors and may lead to cognitive loss in memory, attention, and executive function, as well as slowing down processing speed. A study revealed that doxorubicin an established anti-cancer medication reduced neuronal survival and impaired neuronal plasticity through DNA double-strand breakpoints. However, co-treatment with levetiracetam, an FDA-approved anti-epileptic, improved cell viability of neurons subjected to chemotherapy, decreased doxorubicin induced DNA damage and diminished synaptic and neuritic shrinkage. This implies that levetiracetam may be a hopeful new direction for preventing synaptic loss and reducing cognitive abnormalities in patients with cancer and survivors [34]. Another important cause of cognitive decline in the brain is the synaptic plasticity. Among them, the postsynaptic density protein 95 (PSD95) and synapsin protein (SYP) are associated with synaptic plasticity. However, the proteins probably produced in the hippocampus include those related to microtubule-associated protein 2 (MAP2), synaptic plasticity, and the brain-derived neurotrophic factor (BDNF) pathway, which contributes to the setting of the synaptic plasticity. Besides inducing chromatin condensation and cell membrane fragmentation, doxorubicin also inhibits neurogenesis, based on the decrease in the number of neurons and reduced synapsin immunolabeling that is associated with impaired learning and memory [13].

B. Indirect neurotoxicity of doxorubicin

Possible indirect mechanisms of doxorubicin-induced brain chemotactic action can be summarized:

1) Oxidative Stress and inflammation

Researchers suggest that peripheral inflammation and oxidative stress play a role." partially responsible, for the effects caused by doxorubicin chemotherapy The development of a disease pathway involves the use of doxorubicin containing quinone. A complex structure that can be easily broken down by a human. A lone electron has the ability to transform into semiquinone radicals. The enzyme NADPH cytochrome P450 reductase [54]. works alongside NADPH dehydrogenase. Complex I, which is also referred to complex I and the enzyme xanthine oxidase found in the cytoplasm. The active doxorubicin compound can undergo a chemical reaction, with oxygen. Molecules revert back, to their form as they undergo a transformation. superoxide anion radical (designated as O_2•−). This sequence of events recurs. after administering doxorubicin, a process referred to as the redox cycle takes place. Hydrogen includes O_2•− as a byproduct of oxygen species (ROS). Peroxide (chemical formulaNot Clear Symbol) and hydroxyl radicals (abbreviated as •OH) are known to lead to. Excessive generation of oxygen species (ROS) results in oxidative stress as indicated by studies [59]. The chemical alteration of molecules, through oxidation such as proteins, along with acids and lipids are components, in clinical studies [60]. The rise, in stress induced by doxorubicin was observed. A rise, in protein breakdown and fat oxidation was suggested. As well, as levels of both enzyme activity and non-enzymatic reactions. Antioxidants are beneficial, for health [54]. ROS can activate nuclear transcription factor kB, a redox-sensitive transcription factor, thereby increasing the release of pro-inflammatory cytokines such as tumor necrosis factor alpha

(TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). [61]. In vivo studies show doxorubicin injection increases TNF-a levels in mice, suggesting a cross-talk between oxidative stress and inflammation, contributing to cognitive impairment [62].

TNF-a, a cytokine, can impact the hippocampus volume [63] The lasting enhancing effects of CA1 are inhibited by the hippocampus and dentate gyrus [64]. They are transported into the brain via endothelial cells expressing TNF-a receptors 1 and 2 (TNFR1 and TNFR2) at the blood-brain barrier [65]. TNF-a enters the brain and stimulates astrocytes and microglia, leading to localized synthesis [66]. Binding to TNFR recruits intracellular proteins, triggering inflammatory signaling and nuclear factor-kB NFkB translocation [67]. Inflammatory factors and oxides interact, affecting hippocampus shape and function, causing cognitive impairment. Brain inflammation can down-regulate iNOS expression, causing oxidative and nitrification stress. [69].

2) Nitrification tension

Doxorubicin can induce iNOS expression and elevate nitric oxide levels in the body [67], leading to the formation of peroxynitrite (ONOO), a harmful oxidant. In mice treated with doxorubicin, both NO• and ONOO− cause nitrification by adding a 3-nitrotyrosine to the protein [70]. Manganese superoxide dismutase (MnSOD) is nitrated in mitochondria, resulting in impaired respiratory activity and synergizing with O2•− production [71]. Inflammatory processes and oxidative stress may exacerbate doxorubicin-induced neurotoxicity, leading to neuronal apoptosis in the brain's neurogenic regions. TNF-α activates microglia in the brain, increasing NO production, leading to mitochondrial dysfunction, endoplasmic reticulum stress, and neuronal apoptosis [72]. Treatment with Doxorubicin in rats resulted in enhanced neuroinflammation, oxidative stress, cell death, lipid peroxidation and mitochondrial dysfunction. However, if in combination with Doxorubicin prior administration Galantamine GLN positively influence on molecular markers COX-2, NF-κB, MDA; SODm Bax: Bcl-2 and caspase 3 levels. Enhances the lipid peroxidation and mitochondrial activity also. Neurotoxic action of Doxorubicin therapy could be restored by GLN and suggesting potential utility of GLN in alleviating profound toxic effects induced this drug [73].

III. Increased the therapeutic effect of doxorubicin

(Reduce the neurotoxicity of doxorubicin)

Various strategies have been developed in the past to alleviate the risk of DOX toxicities (neurotoxicity) and therefore enhance therapeutic efficacy through different targeted delivery techniques. Nanotechnology could be used to resolve the limits of cancer therapy, such as systemic adverse effects, and to increase therapeutic efficacy of these drugs by their higher permeability in the tumor tissues. Different building blocks like hydrogels, liposome, metallic nanoparticles, dendrimers and polymeric nanoparticles have been employed for this purpose. Pegylated liposomal doxorubicin (PLDOX) represents a novel preparation of DOX with lipoid characteristics and leads to an increased concentration in tumor tissue due to the enhanced permeability reported for most well vascularized human solid tumors and zero passage into normal tissues, including myocardium. Although free doxorubicin often has fatal side effects, cardiotoxicity is a very uncommon manifestation [74].

This makes PLDOX potentially less toxic to the CNS compared with other anthracyclines. Our results show complete improvements of overall social well-being and cognitive functioning on treatment, whereas patients report the least favoritism for PLDOX as compared to other non-PLDOX regimens regarding cognitive and physical functioning. Nonetheless, these proved to be no more toxic than free doxorubicin [75]. Hydrogels are a form of nanomaterial that can attach the several drug molecules in a polymer molecule used in biomedical applications. They enhance the bioavailability of drug molecules, decrease drug toxicity, prolong circulation time and increase water solubility of lipophilic drugs. For instance, oligo (poly (ethylene glycol) fumarate) (OPF) hydrogels with sodium methacrylate (SMA) were applied for cancer therapy to the human osteosarcoma cell line [76]. It was also found that DOX released from the charged hydrogels maintained its ability to kill cancer cells. In another study, Norouzi et al. [77] employed magnetic iron oxide nanoparticles (IONPs) functionalized through (Unknown) triacetic acid, as a DOX delivery system in glioblastoma multiform treatment. The DOX was released within 4 days and exerts cytotoxicity, proliferation suppression and ROS generation in glioma cell line. This approach enables chemotherapeutics to overcome not only the BBB but also glioma cells along with multidrug resistance and also localized magnetic targeting.

Teleanu et al.'s study [78] revealed that the toxicity of nanomaterials must be evaluated, and still, there is no appropriate and accurate neurotoxicological investigation. This paper concluded that all the nanomaterial types from which the carriers are prepared possess different levels of neurotoxicity, of course, minimum. To avoid or at least substantially minimize neurotoxicity, it is crucial to eliminate hazardous substances from the carriers' matrix, limit the time of their action on the nervous tissue, and regulate their geometrical parameters. Furthermore, the question of whether experimental drugs and clinical drugs can eliminate neurotoxicity induced by DOX is envisaged. This underlines the need for a risk assessment during the process of developing safety in home systems and minimizing the adverse effects profile.

In 2019 El-Agamy et al., have shown that fluoxetine – a selective serotonin reuptake inhibitor (SSRI) – may attenuate DOX induced neurotoxicity among cancer patients. However, the application of SSRI in chemotherapy may not be encouraged because the majority of the subjects undergo particular side effects. As antioxidant treatment is designed to block neurotoxic processes, such an approach can help reduce the impact of chemotherapy on cognitive performance. Some investigational trials have shown that antioxidant therapy could help reduce effects of oxidative stress and neurotoxicity due to chemotherapy. For instance, the xanthone derivative from garcinia mangosteens has demonstrated neuro protective activity by inhibiting DOX elicited oxidative stress as evidenced by the reduced levels of protein carbonyl, nitrotyrosine and 4-hydroxy-2-nonenaladduced proteins in the brain tissue [79].

IV. Conclusions

Although being an efficient chemotherapeutic agent, doxorubicin has been reported a serious side effect of affecting nervous system. Such neurotoxicity causes diverse neurological adverse effects, such as cognitive impairment, neuropathic pain, and motor dysfunction. The neurotoxicity of Doxorubicin is primarily due to oxidative stress, inflammation and neuroinflammation and subsequent apoptosis of neuronal cells. The probable pathways by which chemotherapy reaches the brain get more spacious if different drugs are administered singly or cumulatively. More animal experiments and clinical trials are still required to explain these mechanisms and the theoretical reference for the treatment prevention of post-chemotherapy cognitive dysfunction. Furthermore, there are needs for studies in relation to long-term neurological damage in cancer survivors who were administered with doxorubicin. The studies seeking for new neuroprotective agents or an application of new dosing schemes for doxorubicin or the synthesis of similar nanocomposites that would minimize the neurotoxic impact but maximize the potential therapeutic effects of an anticancer drug are of immense importance.

CONFLICT OF INTEREST

Author declares that he has no conflict of interest.

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