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| RESEARCH ARTICLE

Oxidative Stress Adverse Effects in Histological Changes Induced by Anticancer Drugs: A Review Article

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| ABSTRACT
The imbalance in oxidant burden is defined as oxidative stress (OS), which is the most significant event in the body involved in cancer development and progression. Cancer cells are characterized by high levels of OS and higher oxidant levels. That makes a physician use a double medication strategy to regulate redox status, like pro-oxidant medication and antioxidant supplements. In fact, pro-oxidant drugs have high anti-cancer activities regarding great oxidant levels within cancer cells, while antioxidant medication for redox homeostasis was a failure in some clinical trials. In cancer cells, the redox vulnerability targeted by pro-oxidants ability to produce high-level reactive oxygen species (ROS) is essential for an anti-cancer strategy. Nevertheless, numerous harmful impacts happened by the random targets of uncontrolled therapy stimulate OS in the normal tissues, and the capacity of drug-tolerant of several cancer cells greatly restricted their more implements. The effect of ROS in tissues is revealed by protein oxidation, lipids peroxidation, and DNA mutation; all these changes contribute to histological changes. In the present review, some representative oxidative anti-cancer medications and adverse effects were explained.

| KEYWORDS

Oxidative Stress, adverse effect, Anticancer Drugs.

| ARTICLE INFORMATION

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1. Introduction

Oxidative stress is vital for health in spite of its role in multiple major diseases, including cancer (1). The imbalance in Redox hemostasis, called oxidative stress (OS), was observed in a high frequency in the cancer cells and responsible for almost all cancer cells' malignant behaviors (2, 3); antioxidant medications demonstrated effective activities to inhibit beginning and development of cancer, although of failure in some clinical trials (4-6).

Moreover, some antioxidant therapy was developed to be used in combination with other anti-cancer therapies like radiotherapy chemotherapy (7, 8). Some reports have proposed that cancer cells are killed by chemotherapeutic drugs by ROS accumulation, for instance, cisplatin, doxorubicin, 5-fluorouracil, and arsenic trioxide (ATO) (9, 10). Nevertheless, these drugs have harmful impacts on normal organs and tissues, which are life-threatening(9). It tends to be hemotoxic and causes acute ROS concentration and dysfunction of some endogenous antioxidant defense pathways (11). The effect of ROS in tissues is revealed by protein oxidation, lipids peroxidation, and DNA mutation; all these changes contribute to the histological changes in normal and cancer tissue.

2. Oxidative stress in cancer medications

The state of Biological redox states is non-stable (12). The intracellular redox status regulation is vital to cellular homeostasis maintaining under normal functions (13); the vital mediators of redox reactions represented by ROS, that also considered as cellular respiration byproducts (14), generated from some enzymatic and chemical reactions, like adenine dinucleotide phosphate NADPH oxidase (NOX), nicotinamide cyclooxygenase, iron-catalyzed Fenton pathways and xanthine oxidase (15), with other types as well

as superoxide radicals, hydroxyl radicals, and hydrogen peroxide, and also oxidized lipids, nitric oxide and hydrogen sulfide (16, 17). In general, moderate ROS levels are essential for signaling pathways and physiological activities, whereas higher ROS levels cause cell damage, malignant transformation, and even death (18, 19).

In contrast with this phenomenon, cells have an antioxidant defense system to control the homeostasis of cellular redox and prevent cell injury, which contains endogenous and exogenous antioxidants like N-acetyl cysteine, vitamins (E and C) have demonstrated good antioxidant capacities in preclinical reports (20). The Endogenous antioxidants included catalytic antioxidants, protein enzymes, and tiny scavengers molecules; the antioxidant enzymes are superoxide dismutase, glutathione peroxidase, peroxiredoxin, thioredoxin, glutaredoxin, metallothionein and finally, tiny molecular are glutathione, urate and bilirubin (21).

Cancer cells have high ROS levels due to mitochondrial dysfunction, metabolism alterations, genomic instability, and modifications in the tumor microenvironment (22); thus, cancer cells upregulate mechanisms of antioxidant defense to stabilize the level of ROS within a dynamic range in different ways (23). Chemotherapeutic medications with cytostatic function restrict cancer cells by high production of ROS that leads to triggering apoptosis, autophagy, and ferroptosis.

3. Drugs trigger oxidative stress in cancer medications.

Cancer cells have a more unstable state than normal cells regarding the OS; thus, pro-oxidants are interesting as potential chemotherapeutic agents that directly generate ROS to prevent endogenous antioxidant systems (24, 25). therefore, Different therapeutic approaches were developed, like tiny compounds, chemotherapeutic agents, phototherapy agents, modulate redox metabolites drugs, and drugs' effect on the pathways of signal transferring in redox regulation (26, 27). Even so, the side impacts of pro-oxidant therapy information of drug-induced OS are important to anti-cancer impacts enhancing and clinical implementations expanding. Now, numerous representative drugs that stimulate OS are discussed.

4. Direct ROS stimulation

The treatment strategies for cancer, depending on OS and oxidative injury, have been well proven; some medications effectively restrict cancer cells through excessive ROS production, which is proved by the enhancement of antioxidant activity and decreased cancer-killing impacts (28, 29). Some Chemotherapy treatments that interfere with cell division, like taxanes Vinca and alkaloids, and nucleic acid synthesis like 5-Fluorouracil, anthracyclines, and platinum complexes, can stimulate free radicals generation by mitochondrial injury (30, 31). Anthracyclines are chemotherapy agents as anti-cancer antibiotics that are commonly applied in single or combined with others according to the robust generation capacity of ROS and anti-cancer impacts in different ways. (32), in addition to topoisomerase II poisoning and DNA intercalation (33). Another accepted way of anthracycline is forming an anthracycline-iron complex that causes protein oxidation, lipid peroxidation, and injury in DNA, leading to apoptosis and ferroptosis by ROS generation (34).

ATO (Trisenox™) is a typical pro-oxidant chemotherapy molecule used as a first-line treatment for acute promyelocytic leukemia (35). The toxicity of this drug belongs to the ability to induce OS via different mechanisms, like dissociation, the potential of mitochondrial membrane, GSH deleting, and TRX-1 downregulating (36, 37).

To date, some new therapies (tiny molecule) reused traditional medications have been recorded to have superior pro-oxidant features and marked effects (38, 39). Elesclomol (STA-4783) is a tiny synthetic compound that has an anti-cancer function in several cancers, such as breast cancer and melanoma (40). The mode of action is chelated and transport copper ions to mitochondria, which leads to respiratory chain dysfunction in mitochondria and elevates the cellular OS, leading to cancer cell apoptosis (41). Ivermectin is a wide-spectrum, low-toxicity antiparasitic, and high-efficiency drug. Dou et al. observed the PAK1/Akt axis blocking in breast cancer; it showed an excellent pro-oxidant impact on autophagy by OS in cancer cells (42).

5. Indirect ROS inducers

There is another mechanism of ROS inducers by disrupting intracellular antioxidant systems. The antioxidant processing used ROS neutralizing and the disulfide formation reversing. It depends on the regulation of the two metabolic pathways: GSH and TRX (43). This type of drug includes Drugs that affect GSH metabolism regulate TRX metabolism, modulate NADPH metabolism, and interfere with redox signaling.

5.1. Drugs effect on GSH metabolism

Glutathione (GSH) is a tripeptide consisting of glycine, cysteine, and glutamate; it is almost found as an antioxidant in the cell. The reduced form of GSH is the predominant active state, which consists of about 95% of GSH. Whereas the cells are exposed to ROS, the thiol group of the reduced GSH cysteine is represented as an electron donor to make the GSH disulfide oxidized form (GSSG)

(44). High GSH concentrations are related to independent resistance to chemotherapy and radiation (45). Thus, in cancer cells, one of the interesting therapies to use is to deplete GSH and increase ROS levels to induce OS- cytotoxicity. A study suggested that high GSH levels give oxidative resistance in cancer cells, and depletion of intracellular GSH can overcome treatment resistance and improve cancer medication outcomes (46).

5.2 Drugs regulate TRX metabolism

In addition to the GSH pathway, another drug that is important in the antioxidant system is the TRX-PRX pathway, which intracellular redox homeostasis maintains via redox enzyme regulation, scavenging ROS, and cooperating with GSH redox pathways (47). This system included NADPH and TRX, TRX reductase (TRXR) (48). When the TRX system is prevented from operating OS in the cell, the TRX system inhibition can prevent the development and progression of the tumor via OS increasing, which leads to cancer cell death (49). some TRX system inhibitors have improved as anticancer medication, like selenium compounds, metal complexes, flavonoids, and the penicillin family (50).

5.3. Drugs modulate NADPH metabolism

Both GSH and TRX require reductive production of NADPH to regulate ROS levels in the cell (51). the conversion of GSH to oxidized form through H_2O_2 reduction, then GSSG is returned to GSH form via NADPH-dependent GSH reductase (52). it is also applied in the TRX-S2 generation and thioredoxin reductases 1 & 2 as a substrate (53). Furthermore, the antioxidant capacity of NADPH is represented by binding with catalase (54). Therefore, the limitation of cancer cell capacity to eliminate ROS via NADPH levels regulating leads to cell death (55). Thionicotinamide has a better synergistic effect when used with chemotherapy to elicit tumor cytotoxicity (56).

5.4. Drugs interplay with pathways of redox signaling

The regulation of the Redox state used complex pathways of signal transduction regulation. Many of the essential signaling regulatory pathways like NF-κB, Nrf2-Keap1, and HIF-1 are important in redox homeostasis (57, 58); some medications that interfere with these signals can stimulate the lethal level of OS for cancer treatment, like PX-478 is a tiny agents cause down-regulate HIF-1α and HIF-1 transcription factor function. It is a selective and strong HIF-1α inhibitor that is the cellular response regulator to hypoxia. By HIF-1α inhibiting, PX-478 can decrease the HIF-1 target gene expression, like glucose transporter 1 and VEGF, contributing to glucose metabolism and angiogenesis (59).

5.5 The harmful impacts of anticancer drug-induced oxidative stress

Some clinical drugs have strong anti-cancer functions via OS induction (60). Moreover, the effects of oxidative stress can also damage normal cells and tissue that proliferate rapidly, like bone marrow, gastrointestinal tract, hair follicles, cardiac, hepatic, renal, pulmonary, and gastrointestinal toxicities (61). in addition to the reduction in medication efficacy and stimulating cancer metastasis and recurrence, like OS adaptation in cancer cells, cell cycle modification by OS, or cancer stem cells escape from oxidative injury (62, 63). Thus, the pro-oxidant treatment has two main ways: drug resistance and side effects.

5.6 Oxidative stress of drug-induced organ toxicity

In spite of the good effects of pro-oxidant therapy, it can cause long-term organ damage and dysfunction based on the non-targeted nature of oxidative injury, which can lower the life quality, affect the strategy and completion of chemotherapy systems, and shorten the case lifetime.

5.7 Cardiotoxicity

Both heart disease and cancer lead to human death. The life extension of cancer patients has improved with anticancer drug development; unlucky, these drugs have a higher incidence of cardiovascular adverse effects, like heart failure, endothelial dysfunction, and arrhythmia, that reduce the life quality of patients (64, 65). Numerous reports found the role of OS in the cardiotoxicity of some anti-cancer medication types, such as targeted treatment, chemotherapy, and immunotherapy (66, 67). These events made changes in a therapeutic approach, like dose alteration and interruption or discontinuation in severe cases.

One of the chemotherapy drugs that has induced Cardiotoxicity is Anthracyclines, which cause anthracycline-related cardiomyopathy via DNA injury in mitochondria by OS (68). doxorubicin dose more than (400–700 mg/m^2 for adults) and (300 mg/m^2 for children), cause OS and congestive heart failure(69). semiquinones are a form of Anthracyclines under enzyme catalysis and interplay with oxygen to produce superoxide anion to convert via superoxide dismutase to form H_2O_2, which is stable and low-toxicity; they also react with O_2^- in to produce highly reactive and toxic •OH in the iron-catalyzed Fenton reaction (70). Iron has a role in doxorubicin-induced cardiotoxicity; this reaction also forms reactive anthracycline-iron complexes via Fenton reactions (71). The high level of ROS causes disruption and decreases energy levels that affect the heart muscle, which consumes high energy (72).

5.8 Neurotoxicity

Oxidative stress in the brain and nerves is also reported to have serious impacts on the quality of case life and interfere with the therapeutic system (73). Several Pro-oxidant drugs that generate OS can result in chemobrain features like distraction, executive activity decrement, and memory loss (74). like peripheral or central neuropathy symptoms, as well as spontaneous pain and mechanical/cold allodynia in the extremities (75). The mechanism of inducing Neurotoxicity is still poorly understood because it is more complex (76). Several explanations demonstrated by studies to clarify these mechanisms: dysfunction in mitochondria increased tumor necrosis factor-α level and a high source of ROS generated by translational effects of the drug (77); also, ROS can down-regulate and destruction of the blood-brain barrier via cytokine-mediated signaling downstream causes OS in the brain, in spite of protective mechanisms existence (78). Furthermore, plasma proteins in the blood can be damaged by OS (79). Some drugs have been able to stimulate OS in the peripheral nervous and central system; studies found that cyclophosphamide and doxorubicin elevated protein and lipid peroxidation (80, 81), taxane and cisplatin can stimulate OS in ganglion cells by mitochondrial damage, which causes peripheral neuropathy and cognitive impairment (82).

5.9 Hepatotoxicity

The main cause of discontinuation in preclinical and clinical stages is liver injury (DILI) via some drugs, which is a significant challenge for medicine companies (83). The major metabolism for most chemotherapeutic drugs events represented in the liver that generates excessive ROS levels in the detoxifying xenobiotic and toxic substances course and OS has been elucidated to be associated with liver diseases and other pathological pathways, like hepatotoxicity (84, 85). medications, especially chemotherapy, may lead to endogenous liver injury through specific activity interference or toxic metabolites producing. OS is one of the vital processing of Drug-induced liver injury; these Drugs lead to mitochondrial dysfunction, lipid peroxidation, DNA damage, and ER stress (86). The patients patients treated with low-dose cisplatin have Hepatotoxicity (87). This drug accumulates at a high level in liver cells, which induces hepatotoxicity via oxygen metabolite production. It directly generates H_2O_2 by serious reaction and eliminates some enzyme activity in the antioxidant defense ways, like catalase, glutathione peroxidase, and superoxide dismutase. Moreover, it can link to GSH to make a cisplatin-GSH conjugate, resulting in depletion in GSH and ROS concentration (88). Methotrexate is a folic acid antagonist common in cancers such as acute lymphoblastic, breast cancer, osteosarcoma, non-Hodgkin lymphoma, and leukemia (89) that induces hepatotoxicity (90). Some studies found the intraperitoneal uptake of Methotrexate can cause serum transaminases, bilirubin, and lipid peroxidation to increase and intracellular antioxidant enzyme function reduction, leading to OS-mediated fibrosis and apoptosis in the liver(91, 92).

5.10 Kidney Adverse Effects

The drug-induced OS damage is untargeted in the tissue or organs; the adverse effects can impact multiple systems. Pro-oxidants-caused Kidney dysfunction is a growing concern. According to several reports, the acute kidney injury incidence in cases with chemotherapy elevated by threefold (1.8%–5.2%) between 2007 and 2014 (93). OS has caused impaired kidney function. Drugs like cyclophosphamide, cisplatin, gemcitabine, and MTX (94) produce ROS that elevates OS levels in renal cells and causes fibrosis, tissue injury, and abnormal renal function (95).

Conclusion: from the present review, it can be concluded that anti-cancer drugs have pro-oxidant and anticancer activities, and these features have adverse effects on normal tissue and kill cancer cells; thus, some modification therapy can be used in companies with anticancer drugs like antioxidants molecules to maintain the redox hemostasis.

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