



Chemotherapy-Induced Oxidative Stress and Infertility

Tohid Najafi*

The loss of reproductive function, gonadal dysfunction and infertility are among the most significant adverse effects of chemotherapy. Cancer treatment with DNA alkylating agents, such as cyclophosphamide (CP) and Ifosfamide (IFO) and Cisplatin can lead to gonadotoxicity, impaired fertility, ovarian failure, resulting in premature menopause (1-3).

Generation of free oxygen and nitrogen species by administration of chemotherapeutic agents is known as a sources of their potential deleterious effects on cells. The numerous electrophilic aldehydes that result from oxidative stress-induced lipid peroxidation following chemotherapy can attack cellular targets including ovarian cells. These products of oxidative stress can slow cell cycle progression of malignancies and arrest the cell cycle in a particular checkpoint. The aldehydes are able to inactivate death receptors and inhibit caspase activity and subsequently interfere with drug-induced apoptosis (programmed cell death). These effects would also diminish the efficacy of the cancer treatment (4).

Cyclophosphamide, IFO and cisplatin are common chemotherapeutic alkylating agents with antitumor and immunosuppressant properties widely used in the treatment of malignant neoplasms and some autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus.

Cyclophosphamide (N,N-bis (2-chloroethyl) tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine 2-oxide), alkylates DNA, forming DNA-DNA cross-links that result in inhibition of DNA synthesis and cell death (1); however, it is not specific for cancer cells and will affect all dividing cells, including those in the immune system, reproductive systems, and the gastrointestinal tract. It has been reported that CP-induced ovarian toxicity results in deficits in the formation of oocytes. Based on the evidence of the disruptions in the redox balance through CP functioning as well as the higher release of nitric oxide (NO) during inflammatory conditions, this toxicity is believed to derive from reactive oxygen and nitrogen species (ROS and RNS), in particular, peroxynitrite (ONOO) overproduction when NO couples with superoxide, which appears abundantly in the inflammatory area (5).

Ifosfamide (2H-1,3,2-Oxazaphosphorin-2-amine, N,3-bis (2-chloroethyl) tetrahydro-, 2-oxide) has been shown to interfere with fertility especially in male reproductive

Tohid Najafi, is a senior researcher on reproductive biochemistry at C.S Mott Center for Human Growth, at Wayne State University of Michigan. He is a member of American Society for Reproductive Medicine and his research field focuses on the effect of reactive oxygen and nitrogen species on human infertility. He has comprehensively studied the role of nitric oxide in reproductive system and currently working on controlling the adverse effects of chemotherapy on fertility of cancer patients.



system (2). IFO is a prodrug particular toxic metabolites of which are produced by ring hydroxylation, namely 4-hydroxyifosfamide and acrolein. IFO also undergoes a considerable chloroethyl side chain oxidation and yields chloroacetaldehyde (CAA) which found to be associated with intracellular ATP and glutathione (GSH) depletion. As GSH is an important molecule in the cellular defense system against oxidative stress, administration of IFO may lead to significant diminish in GSH levels and subsequent malfunctioning of antioxidant system. Even though supplementation of GSH seems to be helpful in blocking adverse effects of IFO on reproductive organs, it has been reported that combinations of GSH inhibitors (or other antioxidant inhibitors) with chemotherapeutic medications that cause cell death induced by oxidative stress may prove to be useful for killing cancer cells (6).

Cisplatin (Platinum (4+) chloride azanide) is one of the widely used medication for the treatment of adult cancers. Cisplatin is a highly reactive molecule that binds to RNA, DNA and proteins forming nDNA adducts that are considered as key mediators of cisplatin cytotoxicity. On the other hand, cisplatin accumulates in mitochondria and forms adducts with mitochondrial DNA (mtDNA) and proteins. Mitochondria which function to generate energy by oxidative phosphorylation, are known as one of the main endogenous sources of ROS. Studies reported that exposure to cisplatin leads to a significant increase in intracellular ROS (3). A few others reported that treatment with antioxidants attenuates the cytotoxic effects of cisplatin on different organs, suggesting an involvement of oxidative stress in the pathogenesis of cisplatin-induced cytotoxicity which also seen in reproductive system (7).

The overproduction of ROS and RNS during inflammation leads to an extensive oxidative stress,



cellular injury and apoptosis/necrosis via several mechanisms including peroxidation of membrane lipids, protein denaturation and DNA damage. Oxidative stress may induce reproductive dysfunction and infertility especially by deteriorating oocyte quality. It has been well demonstrated that oxidative stress affects oocyte integrity by disruption of the spindle structure (8), premature primordial follicle activation (9), antral follicle destruction and impairing the oocyte fusibility (9), deficit of mitochondria-derived ATP (10) and induction of postovulatory oocyte aging (11). Aerobic cells have been equipped with a complex antioxidative defense system comprising several antioxidant enzymes the most important of which superoxide dismutases (SODs), glutathione peroxidase (GPx), and catalase.

The exact effects of oxidative stress on cancer initiation, progression and response to chemotherapy requires further investigation. The technologies such as deep DNA sequencing and metabolomics have been recently developed to provide buffers against alteration in the amount of oxidative stress. On the other hand, antioxidants may be helpful to attenuate the adverse effects of oxidative stress. Although there is not a strong evidence to prove direct effect of antioxidants on fertility, they are able to indirectly attenuate oxidative and nitrosative stress applied to reproductive system in the state of malignancy. Nowadays patients with cancer widely use antioxidant supplements after diagnosis or during treatment. These antioxidants in general include compounds with free sulfhydryl groups, including N-acetylcysteine (NAC) and lipoic acid, compounds with multiple double bonds and conjugation and polyphenols, compounds that inhibit reactive oxygen generation as well as xanthine oxidase inhibitors and compounds that induce oxidant defenses (12).

Despite the extensive administration of antioxidants, there is still considerable controversy as to whether modulation of oxidative and nitrosative stress by antioxidant supplementation (such as melatonin, Vitamin E and C, Co-Q10 and etc.) is clinically beneficial or detrimental for fertility preservation in cancer patients. In fact, some investigators have hypothesized that antioxidant supplements have ability to lower the cancer incidence and subside the subsequent chemotherapy-induced reproductive toxicity. They also believe these supplements, by providing protection against toxic side effects, might potentiate chemotherapy and radiation therapy; however some others are even not confident whether reactive oxygen and nitrogen species function to promote or to suppress the cancer (13).

Ethical Issues

Not applicable.

Conflict of Interests

Author declares that he has no competing interests.

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