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REVIEW

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Chemotherapy-induced damage to the ovary and protective strategies

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Abstract

Chemotherapy methods have been well established and cancer survival rates have greatly improved in recent years. However, young female cancer survivors have high risk of losing their fecundity due to ovarian damage induced by chemotherapy [1]. A large number of studies have been performed to understand the mechanisms for how chemotherapy induces ovarian damage, but much remains unknown [2]. In this review, we aim to provide a brief overview of the current knowledge of chemotherapy-induced damage to the ovary and potential protective strategies.

Chemotherapeutic agents and anti-tumor mechanisms

Chemotherapeutic agents have been developed that can inhibit tumor cell proliferation and can induce tumor cell death, and they also play roles in treating chronic inflammatory diseases and in immune inhibition prior to bone marrow transplantation [2]. Chemotherapeutic agents are classified as cell cycle-specific or cell cycle-nonspecific according to the targeted phases of the cell cycle. Cell cycle-specific agents only work against cells in specific phases other than G0 phase, while cell cycle-nonspecific agents target cells in all phases of the cell cycle [3]. Among the wide range of chemotherapeutic agents, those with the highest ovarian toxicity to the lowest are alkylating agents, alkylating-like platinum analogs, taxanes, plant alkaloids, anthracyclines, topoisomerase inhibitors, and anti-metabolites [3]. Representatives of each category are summarized in table 1.

Both alkylating agents and alkylating-like platinum analogs produce intermediates that are highly reactive and can covalently bind to DNA. This induces DNA crosslinks and consequently inhibits DNA transcription and replication [4]. Alkylating agents can also decrease the mitochondrial membrane potential and the accumulation of cytochrome C in the cytoplasm [2], while alkylating-like platinum analogs lead to cell cycle arrest by activating cell cycle checkpoints [5]. Thus both types of agents prevent cell proliferation and induce cell apoptosis.

Texans and plant alkaloids were both originally isolated from plants and act to prevent mitotic spindle formation, which eventually causes cell death [6]. However, they act through different mechanisms. Taxanes prevent spindle formation by binding to tubulin in order to block its depolymerization into microtubules, while plant alkaloids inhibit tubulin polymerization [6].

Anthracyclines are among the most used anti-tumors and antibiotics in chemotherapy. Their mechanism of action is inhibition of the nuclear enzyme topoisomerase II, which leads to the accumulation of DNA fragments that ultimately causes cell death [7]. They also intercalate into double-stranded DNA and disrupt DNA replication. In addition, as a chemotherapeutic agent, anthracyclines lead to mitochondrial disorders by stimulating the production of reactive oxygen species [7]. Other types of topoisomerase inhibitors generate single and double stranded breaks and inhibit microtubule aggregation and interfere with spindle formation thus ultimately inhibiting cell division [8].

Antimetabolites have been widely used as anti-tumor drugs due to their ability to impair the DNA replication machinery either by their direct incorporation into the DNA or by inhibiting the proteins needed for DNA replication and cell division [9].

Other chemotherapy drugs include enzymes, of which the representative is L-asparaginase, which inhibits the function of ribonucleotide diphosphate reductase and limits ribonucleotide conversion and thus interferes with DNA synthesis. Moreover, L-asparaginase can degrade exogenously supplied asparagine, which limits protein synthesis and subsequently leads to cell death [10].

Chemotherapy-induced ovarian damage and its protection

Ovarian damage

The ovary contains different types of follicles according to their states, such as dormant primordial follicles (PMFs) and developing follicles. Because PMFs are quiescent, they are more sensitive to cell cycle-nonspecific agents such as alkylating agents and topoisomerase inhibitors. In contrast, the developing follicles are more vulnerable to cell cycle-specific agents such as anti-metabolites that do not alter the dormant follicle pool [11].

There are three major proposed mechanisms behind ovarian damage caused by chemotherapeutic agents, including apoptosis induced by DNA damage and/or oxidative stress and/or autophagy, over activation of PMFs, and ovarian micro-vessel network damage [3].

Type of agents	Examples	Effects on Cell Cycle	Ovarian damage
Alkylating agents	• Nitrogen mustards (e.g., bendamustine, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan) • Nitrosoureas (e.g., carmustine, lomustine, streptozocin) • Alkyl sulfonates (e.g., busulfan) • Triazines (e.g., dacarbazine, temozolomide) • Ethylenimines (e.g., altretamine, thiotepa)	Non-specific	Primordial follicle Developing follicle
Platinum analogs	• Cisplatin • Carboplatin • Oxaliplatin • Nedaplatin	Non-specific	Primordial follicle Developing follicle
Taxanes and Plant alkaloids	• Vinca alkaloids (e.g., Vincristine, Vinblastine and Vinorelbine) • Taxanes (e.g., Paclitaxel and Docetaxel)	M-phase specific	Developing follicle
Antitumors Antibiotics	• Mitomycin • Bleomycin • Doxorubicin • Valrubicin	Specific and non-specific	Primordial follicle Developing follicle
Topoisomerase inhibitors	• Epipodophyllotoxins • Etoposide • Teniposide	S- and G2-phase specific	Developing follicle
Antimetabolites	• Methotrexate • 5-Fluorouracil • 6-Mercaptopurine • Hydroxyurea	S-phase specific	Developing follicle
Enzymes	• L-Asparaginase	S-phase specific	Developing follicle

Table 1. Characteristics of the chemotherapeutic agents

Diplotene-arrested oocytes in PMFs are more sensitive to DNA damage compared to oocytes at other stages. This is because there are fewer DNA repair responses in PMFs, and as DNA damage accumulates, changes in the expression levels of pro- and anti-apoptotic genes lead to apoptosis [12]. In developing follicles, because their granulosa cells are proliferating, all cytostatic agents can damage them and lead to apoptosis [11].

Oxidative stress caused by chemotherapeutic agents is another factor for inducing apoptosis. The accumulation of reactive oxygen species interferes with microtubule spindle formation and leads to subsequent alterations in chromosome alignment [13], and this along with a decrease in mitochondrial membrane potential [14] leads to DNA damage and mitochondrial dysfunction that ultimately trigger follicle death [15].

Accelerated PMF activation and ovarian reserve exhaustion are other major phenomena related to chemotherapeutic agent-induced ovarian damage. There is evidence that the secretion of primordial follicle inhibitors, for instance, AMH and inhibin-α is greatly decreased due to the treatment of chemotherapy [16]. In addition, the phosphoinositide 3-kinase (PI3K) signaling pathway, which maintains PMF quiescence, has also been found to be activated after chemotherapeutic treatment and to lead to the over activation of primordial follicles [17].

Other mechanisms of chemotherapy induced ovarian damage include autophagy triggered by oxidative stress, nutrient deprivation, hypoxia, and damaged organelles, and similar to apoptosis autophagy appears to play an important role in follicle loss in the ovary [18]. Moreover, the micro-vessel network damage caused by exposure to chemotherapeutic agents leads to decreased blood supply to the ovary, which can induce oxidative stress from ischemia, hypoxia, and nutrient deprivation, and this is followed by DNA damage and apoptosis [19].

Potential protection

Potential protectants against chemotherapy-induced ovarian damage have been intensively investigated in order to protect against PMF depletion, PMF over activation, increased atresia of developing follicles, and damage to the ovarian micro-vessel network. First, anti-apoptosis treatment has been established, including enhancing DNA repair blocking the apoptosis pathway, increasing antioxidants, and preventing the accumulation of chemotherapeutic agents in the nucleus. Second, treatments to inhibit PMF over activation have been investigated, for instance, blocking the PI3K signaling pathway, replenishing AMH, and adding immunomodulator ammonium-trichloro (0,0-dioxyethylene) tellurate, melatonin gonadotropin-releasing hormone analogues, or tamoxifen to the treatment regimen [3]. Third, granulocyte colony-stimulating factor has been used as a co-treatment with chemotherapy and been found to effectively decrease micro-vessel loss in the ovary but not to interfere with the anti-tumor effect of chemotherapy [20]. Fourth, Gonadotropin-releasing hormone (GnRH) agonists has been used to protect the ovary from chemotherapy by suppressing ovarian functions in clinical practice but with controversy. Some favored the use of GnRH agonists by reducing the risk of early menopause and improving prospects for fertility [21] while others reported no improvement on the preservation of ovarian functions [22]. Other strategies are also under investigation, including caloric restriction, gene therapy, pharmaceutical development, improvements in chemotherapy, and the regeneration of damaged cells in the ovary using stem cells, including human amniotic fluid cells, human amniotic epithelial cells, and bone marrow-derived mesenchymal stem cells [3].

In conclusion, great advancements have been made in the last decade in elucidating mechanisms of chemotherapy-induced ovarian damage and potential protective strategies against such damage. However, it remains unclear which is the most critical mechanism or what signaling pathways play a more important role. Moreover, molecules as targets to block the negative effects induced by chemotherapeutic agents still need to be identified. With more well-designed basic research and clinical trials, the balance between the efficacy and safety of chemotherapy is expected to be achieved and that ovary-sparing treatment can be provided along with effective therapeutic interventions in the clinic in the near future.

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