Chemotherapy-Induced Ovarian Damage and Fertility Preservation

Subjects: Agricultural Engineering
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Definition

Chemotherapy-induced ovarian damage and fertility preservation in young patients with cancer are emerging disciplines. The mechanism of treatment-related gonadal damage provides important information for targeting prevention methods.

1. Introduction

It is estimated that 9.2 million women were newly diagnosed with malignancy worldwide in 2020 [1]. Among adolescents and young adults aged 15–39 years, 89,500 patients were newly diagnosed with cancer, and 9270 mortalities were reported in the United States [2]. In these patients, oncologic therapies can harm normal ovarian function and result in ovarian damage [3]. Fertility preservation is now an emerging discipline that plays a critical role in preventing infertility in the care of young cancer patients [4][5].

Chemotherapy could harm gonadal function in young cancer patients and cause loss of the ovarian reserve [6]. The molecular mechanism of chemotherapy-induced ovarian damage has been investigated to understand and prevent gonadotoxicity in cancer treatment [7]. However, the genetic aspects of chemotherapy-induced ovarian damage are still not fully understood. This article reviews the genetics of chemotherapy-induced ovarian dysfunction and explores the gene-targeted prevention of ovarian damage.

2. Mechanism of Chemotherapy-Induced Ovarian Damage

Chemotherapy-induced ovarian damage may be transient, and menstruation may recover after treatment completion. Oocytes and granulosa cells are vulnerable to chemotherapeutic agents. The possible gonadotoxic chemotherapeutic agents used are shown in **Table 1** [7]. Each agent has a different mechanism of action on malignant cells, resulting in the cessation of the cell cycle. With conventional chemotherapy agents, ovarian insufficiency involves PF pool depletion by apoptosis or hyperactivation mechanisms, mediated by the ABL/TAp63 and PI3K/Akt/mTOR pathways [7].

Table 1. Ovarian damage with chemotherapeutic agents and their mechanisms of action.

Type of Chemotherapy	Agents	Target Disease	Mechanisms of Action
Alkylating agents	Cyclophosphamide Ifosfamide Nitrosoureas Chlorambucil Melphalan Busulphan Mechlorethamine	Leukemia, breast cancer, lung cancer, ovarian cancer, prostate cancer, lymphoma, Hodgkin's disease	Interference with cell division via cross-linking of DNA; Mitochondrial transmembrane potential reduction; Inhibition of the accumulation of cytochromec in the cytosol; Induction of DSBs in oocytes

Type of Chemotherapy	Agents	Target Disease	Mechanisms of Action
Vinka alkaloids	Vinblastine Vincristine	Testicular cancer, lymphoma, Hodgkin's disease, breast cancer, germ cell tumors, lung cancer,	Inhibition of tubulin forming into microtubules; Low gonadotoxic risk
Antimetabolites	Cytarabine Methotrexate 5-fluorouracil	Leukemia, breast cancer, ovarian cancer, gastrointestinal cancer	Inhibition of purine, pyrimidine becoming incorporated into DNA; Inhibition of RNA synthesis; Low gonadotoxic risk
Platinum agents	Cisplatin Carboplatin Oxaliplatin	Bladder cancer, colorectal cancer, head and neck cancer, lung cancer, ovarian cancer, testicular cancer	DNA damage by the formation of DNA adducts, which interfere with cellular transcription and replication, leading to oocyte death.
Anthracycline antibiotics	Daunorubicin Bleomycin Doxorubicin	Lymphoma, leukemia, breast cancer, sarcoma	Intercalation with DNA and prevention of its replication and transcription via the inhibition of topoisomerase II; Upregulation of P53 protein which induces apoptosis; DNA DSBs leading to activation of ATM, which initiates apoptosis
Others	Procarbazine	Hodgkin's disease, brain tumor	Inhibition of DNA methylation and RNA and protein synthesis

DSB, double-strand breaks.

2.1. Chemotherapy-Induced DNA DSBs

Chemotherapy can result in DSBs in DNA that can be repaired by the ataxia-telangiectasia mutated-mediated DNA damage repair pathway. However, failure of the repair pathway results in cellular apoptosis in growing follicles and proliferating granulosa cells [8]. P63 protein, a transcriptional factor implicated in cancer and development, is also involved in female reproduction [9]. TAp63, which is the N-terminal transactivation domain containing isoform of P63, is responsible for the protection of the female germ line during meiotic arrest [10]. The P63 protein activates BAX and BAK proteins, which can be transmitted by activating Tap73, a P53-upregulated modulator of apoptosis [11]. This damage has been reported to occur even with low-risk gonadotoxic agents [12].

2.2. Burnout Effect

The PI3K/Akt/mTOR pathway directly influences the oocytes and pre-granulosa cells of PFs and indirectly destroys large follicles, called the "burnout effect" [13]. This phenomenon impairs anti-Mullerian hormone (AMH) and reduces the suppression of the PF pool through destroying follicles, which is followed by the activation of PFs to compensate for the decrease in the number of growing follicles [14]. This effect triggers the growth of dormant follicles. It is affected by the upregulation of the PI3K/Akt/mTOR pathway and substantial follicular apoptosis, which reduces AMH secretion [15].

2.3. Stromal and Microvascular Damage

The ovarian stroma can be indirectly damaged by chemotherapeutic agents [16][17]. A previous study

reported chemotherapy-induced ovarian stromal fibrosis and vascular damage [18]. Damage to blood vessels and focal fibrosis of the ovarian cortex could be another mechanism of chemotherapy-induced ovarian dysfunction [19]. In patients undergoing chemotherapy, the ovaries show thickening and hyalinization of the cortical vessels [20]. This is also supported by another study that showed an inverse correlation between ovarian vascular density and follicular apoptosis [21], thus suggesting an indirect mechanism by which chemotherapy-induced ovarian vascular injury reduces the number of PFs.

2.4. Genes Related to Chemotherapy-Induced Ovarian Damage

2.4.1. DNA Damage Repair

Homologous or non-homologous DNA repair is involved in the recovery of chemotherapy-induced DNA damage in PFs. Consequently, mutations in genes that regulate these repair pathways could increase the susceptibility to ovarian toxicity due to chemotherapy.

Brca1 and Brca2 are critical in the repair of DNA DSBs. Brca mutation carriers have not only increased the risk of cancer but also fertility-related issues [22]. Brca1 mutation carriers show lower AMH levels, but the results are contradictory between studies [23][24]. Brca2 mutations are not associated with a low ovarian reserve in these studies. On the other hand, a retrospective study on the in vitro fertilization of Brca mutation carriers showed no significant differences in the procedure cycles or in the number of oocytes compared to non-carriers [25]. Additional research is warranted to define exact role of Brca mutation in fertility preservation in patients with related malignancy. In cancer patients with Brca mutations, poly (ADP-ribose) polymerase (PARP) inhibitors is widely used for the treatment of cancer [26]. The use of PARP inhibitors could negatively affect embryo development [27]. In another study, the gene expression of granulose cell markers was decreased in patients with PARP inhibitor use [28].

Alterations of other genes involved in DNA repair, Mcm8 and Mcm9, can induce primary ovarian insufficiency [29]. Stag3, a meiosis-specific gene, is also important in DNA damage repair. A recent study demonstrated that variants of Stag3 are associated with primary ovarian insufficiency [30]. Similarly, Hfm1, Nup107, and Syce1 are associated with DNA repair and are implicated in ovarian insufficiency [31][32][33].

2.4.2. Apoptosis

Dysregulation of apoptosis results in decreased ovarian reserve and an increased possibility of gonadal damage after chemotherapy. Nanos3, which expresses an RNA-binding protein that regulates apoptosis to maintain a proper PF pool, was related to ovarian insufficiency in a study of Chinese women with variant mutations [34]. In that study, the level of NANOS3 protein was correlated with the number of PGCs. Ablation of another important anti-apoptotic gene, Bcl2, is related to a decreased number of PGCs in mice [35]. Pgrmc1, which is another candidate gene, has a progesterone-dependent anti-apoptotic action, which is another candidate gene. Mutations in this gene were related to ovarian insufficiency in a previous study [36][37].

2.4.3. Follicular Activation and Development

The possibility of ovarian damage after chemotherapy could also be increased because of genetic mutations involved in follicular activation and development. Foxo3a inhibits follicular activation in the ovary. Ablation of this gene in mice is related to early ovarian dysfunction [38]. In humans, Foxo3a and Foxo1a were identified in women with primary ovarian insufficiency in two studies [39][40]. Variants of another follicle developing gene, Bmp15, are associated with ovarian dysfunction, as identified in multiple studies [41][42][43].

3. Prevention Strategy for Ovarian Damage

Fertility preservation options can be personalized in terms of patient age, desire for conception, treatment regimen, and socioeconomic status [44]. Such options include hormonal medications for ovarian

suppression, cryopreservation, in vitro oocyte maturation, artificial ovaries, and stem cell technologies. Additionally, the potential ovarian protective effects of several genetic variants could be considered. Several established options including embryo cryopreservation and oocyte cryopreservation are already in clinical use. However, there are also experimental options including ovarian tissue cryopreservation, oocyte in vitro maturation, artificial ovary, and stem cell technologies [44].

A protective effect of reduced allele frequency of the Inha gene promoter was observed in patients with premature ovarian insufficiency [41][42]. In a study involving ovarian insufficiency, increased expression levels of Mvh , Oct4 , Sod2 , Gpx , and Cat were detected after resveratrol treatment [45], implying that genes related to ovarian stem cell proliferation or anti-oxidative processes may help protect the ovary against chemotherapy-induced damage. An association between microRNA polymorphisms and the risk of premature ovarian insufficiency was also reported previously. Further investigations are warranted to identify significant protective genes against chemotherapy-induced ovarian damage.

Traditional biochemical markers for ovarian reserve include AMH level, follicle-stimulating hormone concentrations, inhibin-B level, and antral follicle count on ultrasound [7]. However, due to the development of genetic testing, several candidate genes for ovarian insufficiency are being investigated [36]. Fmr1 and Brca testing can be performed easily in genetic clinics. Patients with mutations in these genes are at a higher genetic risk at baseline [46]. Evaluation of other frequent genetic variants, including Nobox , Figla , Bnc1 , Sohlh1 , Sohlh2 , Foxo3 , and Hfm1 , could help identify individuals with increased genetic risk of ovarian damage due to chemotherapy. Next-generation sequencing could be considered in ovarian reserve testing by using targeted gene panels, whole-exome sequencing, or whole-genome sequencing [47]. The application of this technique is the future of genetic evaluation of patients who are at high risk of ovarian dysfunction after chemotherapy.

Ovarian tissue cryopreservation could be considered for fertility preservation in children or young patients with cancer who need immediate treatment and do not have enough time for ovarian stimulation. Using this technique, a large number of oocytes can be preserved, and the hormonal functions of the ovary can be protected [48]. Slow freezing has been established as the preferred method for ovarian tissue cryopreservation rather than vitrification [49]. Ovarian activity was restored in 92.9% of the cases after transplantation of cryopreserved ovarian tissue by using the slow-freezing method [50]. Owing to the possible contamination of the ovarian tissue with malignant cells, this procedure is not utilized for patients with ovarian or hematologic malignancies [51][52].

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Keywords

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